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(54) Title: PREPARATION OF EMULSIONS AND CONCENTRATES THEREOF

(57) Abstract: The invention provides a process for the preparation of a liquid emulsion composition having a continuous aqueous phase containing a gelling agent and a thickener and optionally a physiologically tolerable amount of at least one water soluble vitamin and/or non-vitamin drug, and a discontinuous oil phase, optionally comprising at least one lipophilic vitamin and/or non-vitamin lipophilic drug and optionally an edible triglyceride, said emulsion composition further containing at least one emulsifying agent, said process comprising: forming an aqueous composition comprising an aqueous solution of a gelling agent and a thickener and optionally at least one water soluble vitamin and/or non-vitamin drug; forming a water-immiscible liquid composition comprising at least one emulsifying agent and optionally at least one lipophilic vitamin and/or non-vitamin drug; mixing said water-immiscible composition with at least part of said aqueous composition whereby to form an oil-in-vater emulsion; and if required mixing further components with said emulsion whereby to form said liquid emulsion composition.

Preparation of emulsions and concentrates thereof

This invention relates to emulsions and concentrates thereof, for example, drug-containing formulations in liquid and dried forms, for example a syrup, a liquid concentrate, a powder or a tablet, and a process for their manufacture optionally including spray or freeze drying.

Many compositions, e.g. pharmaceuticals, cosmetics, nutraceuticals, etc. need to be formulated as emulsions, generally due to a necessary component being substantially water-insoluble or to the preference of the consumer for a liquid rather than a solid dosage form.

However formulating products in emulsion form raises its own problems, for example the stability of the emulsion itself and of its components, and the increased volume of an emulsion relative to a concentrated, solid formulation results in increased storage and transport expense.

In the case for example of vitamin-containing compositions (e.g. food supplements or nutraceuticals), formulation as a liquid composition with extended storage or shelf-life however provides its own problems, in particular relating to the stability of the vitamins. Vitamins in liquid dosage forms are easily degraded mainly due to the influence of temperature, moisture, oxygen, light and pH. The presence of other vitamins will also influence the degradation pattern of each individual vitamin which complicates the formulation task even further. It is also important to realize that it is the stability of the most unstable component which determines the overall shelf-life of a product.

The problem posed by the instability of vitamins in liquid formulation is highlighted in "Oil and Water-

Soluble Vitamins: Oral Solution" in the monograph for Nutritional Supplements in USP 24 which states that supplements should contain not less than 90% and not more than 250%, 150% or 450% of the labelled amounts of certain vitamins. Thus vitamin compositions generally contain more than the labelled amounts of certain vitamins to allow for degradation during storage and so meet the legal requirement that the vitamin content must be at least as high as indicated on the product label throughout the shelf-life of the product. While vitamin degradation may thus be compensated for, to some extent, by use of an overage, the overage should desirably be relatively small otherwise doses received when using relatively fresh product would be well above the desired level. The USP monograph thus sets out limits for the vitamin content in a liquid formulation which are undesirably wide from a legal and cost perspective. Much narrower limits are clearly desirable. There is thus a general need for a manner of producing emulsions or emulsion concentrates which have enhanced stability, and where appropriate enhance the stability of any degradable components for which the emulsion is a vehicle.

We have now found that oil-in-water emulsion compositions with very long storage lives can be produced using a combination of an emulsifier, a gelling agent and a thickener as well as water and a water-immiscible liquid.

We have also found that such stable emulsions may successfully be concentrated (e.g. by drying) and subsequently reconstituted.

Thus viewed from one aspect the invention provides a process for the preparation of a liquid emulsion composition having a continuous aqueous phase containing a gelling agent and a thickener and optionally a physiologically tolerable amount of at least one water soluble vitamin and/or a non-vitamin drug, and a

discontinuous oil phase, preferably comprising at least one lipophilic vitamin and/or non-vitamin drug and optionally an edible triglyceride, said emulsion composition further containing at least one emulsifying agent, preferably one selected from edible phospholipids and fatty acid esters, said process comprising:

forming an aqueous composition comprising an aqueous solution of a gelling agent and a thickener and optionally at least one water soluble vitamin and/or non-vitamin drug;

forming a water-immiscible liquid composition comprising at least one emulsifying agent and optionally at least one lipophilic vitamin and/or non-vitamin drug;

mixing said water-immiscible composition with at least part of said aqueous composition whereby to form an oil-in-water emulsion; and

if required mixing further components with said emulsion whereby to form said liquid emulsion composition, e.g. mixing in further aqueous or non-aqueous compositions containing a physiologically tolerable mineral (e.g. iron, zinc) compound, sweeteners, a further gelling agent or thickener, further vitamins, non-vitamin drugs, minerals, flavours, colours, preservatives etc.

Preferably at least one vitamin and/or non-vitamin drug should be present. More preferably at least one vitamin should be present.

Viewed from a further aspect the invention provides a liquid emulsion composition having a continuous aqueous phase containing a gelling agent, e.g. agar agar, and one or more gum, for example, a plant gum, and optionally a physiologically tolerable amount of at least one water soluble vitamin and/or non-vitamin drug, and a discontinuous oil phase preferably comprising at least one lipophilic vitamin and/or non-vitamin drug and optionally an edible triglyceride, said emulsion composition further containing at least one emulsifying

agent, preferably one selected from edible phospholipids and fatty acid esters, said oil phase comprising at least one of (i) droplets of a discontinuous aqueous phase containing a physiologically active or beneficial compound dissolved therein, (ii) an inorganic particulate, and (iii) a non-vitamin lipophilic drug compound.

In the case of a multivitamin and mineral-containing emulsion, the major proportion (i.e. at least 50% wt) of the oil phase in the compositions of the invention preferably comprises an edible oil (e.g. an edible triglyceride) and/or vitamin E. Vitamin E is especially preferred. Further lipophilic vitamins may be present in the oil phase. In the case of a drug-containing emulsion the vitamins may be replaced by a non-vitamin lipophilic drug compound.

In the compositions of the invention, when present, the edible triglyceride is preferably a fish oil or more preferably a plant oil, optionally wholly or partially hydrogenated, e.g. coconut oil, soyabean oil, rape seed oil, sunflower oil, safflower oil, mustard seed oil, olive oil, peanut oil, etc. Particularly preferably the oil will be one rich in relatively short fatty acid chains, e.g. having a high abundance of C_6 to C_{18} or more preferably C_8 to C_{12} fatty acid residues. Particularly preferably, the weight average fatty acid carbon content is in the range C_8 to C_{12}. Alternatively, the oil will be one rich in long fatty acid chains, e.g. having a high abundance of C_{16} to C_{22} or particularly C_{18} to C_{22} fatty acid residues, especially C_{18}. Fatty acid profiles can be adjusted as desired by fractionating plant oil or by mixing plant oils from different sources. Highly unsaturated fatty acids are in general not preferred.

The oil phase, e.g. the edible triglyceride when present and vitamin E or a non-vitamin lipophilic drug substance, together preferably constitute up to 20% by weight of the total composition, for example, up to 10%,

more preferably up to 5% by weight of the total composition, more especially preferably up to 3% by weight, still more preferably up to 1% by weight, e.g. 0.05 to 0.5% by weight.

The vitamin E used according to the invention may be in any of the forms in which vitamin E may be presented including derivatives, analogues, metabolites and bioprecursors, e.g. α-tocopherol, α-tocopherol acetate, α-tocopherol acid succinate, vitamin E TPGS and tocotrienol. However α-tocopherol acetate, and especially d,l-α-tocopherol acetate, is preferably used. The vitamin E and the edible triglyceride (when present) are preferably present in a weight ratio of 1:100 to 100:1, more preferably 20:80 to 98:2, still more preferably 75:25 to 95:5, especially 85:15 to 93:7 or vitamin E should provide 80-120% of its recommended daily allowance.

The emulsifying agent used in the compositions of the invention is preferably a phospholipid. However in place of, or in addition to, the phospholipid other fatty acid ester emulsifying agents may be used, e.g. esters of fatty acids (e.g. C_{16-22}, especially C_{18} fatty acids) and polyhydric alcohols (especially C_6 alcohols) or polyoxyethylated derivatives thereof, in particular the span and tween non-ionic surfactants, especially polysorbate 80 (i.e. Tween® 80), ethoxylated/ propoxylated block polymers, for example, poloxamers, alkylpolyglycosides, and polyacrylic acid polymers, for example, Carbopol and Pemulen type emulsifiers. Nonetheless, while such emulsifiers, in particular polysorbate 80, have found use in the pharmaceutical and dietary supplement area, they are not generally preferred for use in foodstuffs and the use of phopholipids in the compositions of the invention is preferred.

The phospholipid used in the compositions of the invention is preferably a glycerophospholipid, a

lysophospholipid or a sphingophospholipid, e.g. a sphingomyelin (SPH), cerebroside or ganglioside. Examples of glycerophospholipids include phosphatidic acids (PA), phosphatidylethanolamines (PE), phosphatidylcholines (PC), phosphatidyl-glycero-phosphates, N-acyl-phosphatidyl-ethanolamines, phosphatidylserines (PS), phosphatidylinositols (PI), phosphatidylglycerols, diphosphatidylglycerols and plasmalogens. Examples of lysophospholipids include lysophosphatidylcholines, lysophosphotidylethanolamines, lysophosphatidylinositols, lysophosphatidylserines, lysophosphatidylglycerols, lysophosphatidylglycerophosphates, lysodiphosphatidylglycerols, lyso-N-acyl-phosphatidylethanolamines and lysophosphatidic acids, Glycerophospholipids, for example phosphatidylcholines, are particularly preferred. The phospholipid may be naturally occurring, synthetic or semisynthetic; however arian egg phospholipids or plant-derived natural phospholipids such as lecithins are especially preferred, e.g. soyabean, sunflower, rapeseed, corn or peanut lecithins. By semisynthetic phospholipids is meant a natural phospholipid which has been subjected to chemical modification, e.g. hydrolysis, for example enzymatic hydrolysis with phospholipases such as phospholipase A_1, A_2, B, C, or D, especially phospholipase A_2. Single phospholipids or combinations of two or more phospholipids may be used. Plant derived lecithins generally contain a mixture of phospholipids, e.g. PC together with one or more of PE, PI, PS, PA and SPH. One example of a particularly suitable commercially available food grade phospholipid is Emultop (available from Lucas Meyer GmbH, Hamburg, DE), a deoiled, enzymatically hydrolysed, powdered soybean lecithin enriched with lysophospholipids. Lecithins are also particularly preferred for use as the phospholipids due to their tocopherol content and inherent

antioxidative properties.

The emulsifying agent, e.g. the phospholipids or fatty acid ester emulsifiers, are preferably used in the preparation of both the aqueous and oil phases before subsequent emulsification. The weight ratio of emulsifying agent to the total oil phase is preferably 1:3 to 1:25, more preferably 1:5 to 1:20, more preferably 1:7 to 1:15, especially 1:8 to 1:12.

Alternatively, the weight ratio of emulsifying agent to the total oil phase is 1:5 to 1:200, more preferably 1:10 to 1:100, especially 1:12 to 1:70.

It is thought that the phospholipid or fatty acid ester provides the oil droplets in the emulsion with an at least partial surface membrane which serves to promote stability both of the emulsion and of the vitamins, and/or non-vitamin lipophilic drugs dispersed in the droplets. The protection of the lipophilic vitamins and non-vitamin drugs may arise as a result of reduced oxygen diffusion across the oil-water interface of the emulsion droplets and desirably the concentration of the vitamins other than vitamin E in the oil phase is relatively low in order to have a low ratio between their in-oil concentration and the oil-water interface surface area.

The lipophilic or hydrophilic vitamins, or non-vitamin drugs, or other agents (i.e. minerals) present in the composition, may be incorporated into particles or droplets (e.g. droplets of deoxygenated water solution) within the oil phase droplets in the emulsion. The particles or droplets may have a small diameter e.g. 1 to 1000 nm, preferably 5 to 800 nm, especially 10 to 600 nm. The particles or droplets would therefore be protected from exposure to oxygen. Thus, a water-in-oil-in-water emulsion is also considered in the emulsion of the invention.

The lipophilic vitamins suitable for use in the invention include vitamin E, vitamin A, vitamin K and/or

vitamin D, especially vitamin A, vitamin D and vitamin E, particularly vitamin E. However, any one of these vitamins, or any combination of the foregoing, would be suitable for use in the composition of the invention.

The vitamin D used in the compositions of the invention may be in any one of its various active forms including derivatives, analogues, metabolites and bioprecursors, e.g. cholecalciferol (vitamin D_3), ergocalciferol (vitamin D_2), 1α,25-dihydroxy vitamin D, 25-hydroxy vitamin D, 1α-hydroxy vitamin D, etc. Ergocalciferol and, even more so, cholecalciferol are preferred. Vitamin D_3 is readily available commercially in an edible oil base, e.g. from Roche. Such forms may include edible triglycerides and it should be noted that the total quantity of edible triglycerides in the composition may include some deriving from the vitamin D mix.

The vitamin A used in the compositions of the invention may be used in any of its various active forms including analogues, derivatives, metabolites and bioprecursors e.g. retinols, esters of retinol, dehydroretinol and beta-carotene. Most preferred in the composition of the invention is retinol.

The vitamin K used in the compositions of the invention may be used in any of its various active forms including analogues, derivatives, metabolites and bioprecursors, e.g. phytonadione, menaquinone and menadione.

The water-soluble vitamins suitable for use in the composition of the invention include thiamine, riboflavin, niacin, nicotinamide, Vitamin B_6 group, biotin, pantothenic acid, folic acid, pyridoxine, pyridoxal, pyridoxamine, inositol, vitamin B_{12}, choline and/or ascorbic acid. Any one of these vitamins, or any combination of the foregoing, may be used in the composition of the invention.

Nicotinamide (also known as a B complex vitamin)

may be used in any available active forms, including analogues, derivatives, metabolites and precursors.

Thiamine (vitamin B_1) may be used in any available active form, including analogues, derivatives, metabolites and precursors. Preferred forms include thiamine pyrophosphate, thiamine hydrochloride and thiamine mononitrate.

Riboflavine (vitamin B_2) may be used in any available active form, including analogues, derivatives, metabolites and precursors. Preferred forms include riboflavine, riboflavine 5' phosphate and riboflavine 5' phosphate sodium.

Pantothenic acid (a B complex vitamin) may be used in any available active form, including analogues, derivatives, metabolites, precursors and as a salt. As a salt, dexpanthenol is preferred.

Pyridoxine (a vitamin B_6) may be used in any available active form, including analogues, derivatives, metabolites and precursors. (Other B_6 vitamins include pyridoxal and pyridoxamine, which can also be used in the composition of the invention.)

Folic acid (a B complex vitamin) may be used in any available active form, including analogues, derivatives, metabolites and precursors.

Ascorbic acid (vitamin C) may be used in any available active form, including analogues, derivatives, metabolites, precursors and as a salt, especially sodium, potassium or calcium ascorbate.

Certain of the vitamins have relatively low water solubility, e.g. riboflavin and folic acid, and these may be included in the compositions of the invention in dispersed rather than fully dissolved form.

Preferably the composition of the invention will contain vitamins and/or minerals in the range of 15 to 500% of the Recommended Daily Allowance (RDA), preferably 30 to 200% RDA, especially 80 to 120% RDA per dose. The RDAs as specified in the Council Directive of

24 September 1990 on nutrition labelling for foodstuffs (90/496/EEC) are as follows:

Vitamin A:	800 μg
Vitamin D:	5 μg
Vitamin E:	10 mg
Vitamin C:	60 mg
Thiamin:	1.4 mg
Riboflavin:	1.6 mg
Niacin:	18 mg
Vitamin B_6:	2 mg
Folic acid:	200 μg
Vitamin B_{12}	2 μg
Biotin:	0.15 mg
Pantothenic acid:	6 mg
Vitamin K:	50 μg

The recommended daily amounts of vitamin B_{12} and vitamin K are taken from "Nordic guidelines for intake of nutrients, 1996".

An overage of vitamin may be used in the composition of the invention, in order to compensate for any degradation. However, the vitamins used in the composition of the invention are relatively stable, and therefore only small overages, in the range of 0 to 25%, preferably 0 to 15%, more preferably 0 to 10%, e.g. 5 to 10% may be used.

An overage of 10% of vitamins A and D will ensure a shelf-life of 18 months at room temperature. An overage of 5% of vitamin E (DL-α-tocopheryl acetate) ensures the same shelf-life. The following overages may be used for the water-soluble vitamins: thiamine nitrate (10%), nicotinamide (5%), ascorbic acid (25%), pyridoxine hydrochloride (5%), dexpanthenol (10%), vitamin B_{12} (20%), riboflavine (5%) and folic acid (20%).

Desirably, the compositions of the invention contain: optionally 120 μg to 4000 μg, preferably 640 μg

to 960 μg vitamin A; optionally 0.75 μg to 25 μg, preferably 4 μg to 6 μg vitamin D; optionally 9 to 300 mg, preferably 48 to 72 mg vitamin C; optionally 0.21 mg to 7 mg, preferably 1.12 mg to 1.68 mg Thiamin (vitamin B1); optionally 0.24 mg to 8 mg, preferably 1.28 mg to 1.92 mg Riboflavin (vitamin B_2); optionally 2.7 mg to 90 mg, preferably 14.4 to 21.6 mg Niacin (vitamin B_3), optionally 0.3 to 10 mg preferably 1.6 mg to 2.4 mg Pyridoxine (vitamin B_6); optionally 30 μg to 1000 μg preferably 160 μg to 240 μg folic acid (vitamin B_9); optionally 0.6 μg to 6 μg, preferably 1.6 to 2.4 μg, vitamin B_{12}; optionally 0.225 mg to 0.75 mg, preferably 0.12 to 0.18 mg biotin; optionally 0.9 mg to 30 mg, preferably 4.8 mg to 7.2 mg pantothenic acid (vitamin B_5); and/or 7.5 μg to 250 μg, preferably 40 μg to 60 μg vitamin K.

Besides the lipophilic vitamins/non-vitamin drugs, the optional water-soluble vitamins, the emulsifying agent (e.g. phospholipid), the gelling agent and the thickener and water, the compositions according to the invention may, and indeed generally will, contain other physiologically tolerable components, for example sweeteners, starches, antioxidants, isoflavones, beta-carotene, lycopene, soluble and insoluble fibre, minerals (e.g. zinc or iron), colouring agents, pH modifiers (e.g. buffering agents or acidifiers, for example citric acid, lactic acid, malic acid, etc.) preservatives (e.g. benzoates and sorbates), flavours, etc.

The compositions of the invention contain a viscosity modifier, i.e. a material which increases the viscosity of the aqueous phase, most preferably the combination of a thickener (for example, a gum) and a gelling agent, for example the combination of agar agar and an edible gum such as locust bean gum, guar gum, xanthan gum, gum arabic, or gum tragacanth. Other examples of thickening agents include cellulose

derivatives, for example, methyl cellulose, carboxymethylcellulose, hydroxypropylcellulose, methyl hydroxypropylcellulose and hydroxypropylmethylcellulose and modified starches based on maize, waxy maize, potato, wheat, rice and tapioca. The gelling agent and the thickener combination will generally be used at total concentrations of 0.01 to 5% w/w of the total liquid emulsion composition, more preferably 0.05 to 3% w/w, especially 0.1 to 1.5% w/w. The gelling agent and the thickener combination serve to enhance the physical stability of the emulsion. A gelling agent is defined as being a material capable of forming a gel on dissolution in water. Examples of gelling agents include alginates, more specifically Na-alginate, K-alginate, NH_4-alginate, Mg-alginate or Ca-alginate, propylene glycol alginate, carrageenans, more specifically kappa-carrageenan, iota-carrageenan or lamda-carrageenan, gellan gum, more specifically high acyl gellan gum or low acyl gellan gum, pectins, more specifically high methoxyl pectin or low methoxyl pectin and gelatin, more specifically gelatin of animal or fish origin. The gelling agent is preferably used at a concentration of 0.02 to 1% w/w of the total composition, more preferably 0.03 to 0.4% w/w, especially 0.04 to 0.3% w/w. One particularly preferred gelling agent is agar agar and this is especially preferably used together with one or more edible gums, e.g. locust bean gum and guar gum. The thickener is preferably used at a concentration of 0.05 to 1.5% by weight of the total composition.

The compositions of the invention are intended for oral ingestion. For oral ingestion, the compositions desirably contain sweeteners and flavours to enhance their acceptability to the consumer. The sweeteners used may be natural sweeteners, e.g. mono, di and polysacchrides, for example sucrose, fructose, fructooligosaccharides (oligofructoses), glucose,

glucose syrup, invert sugar, maltodextrins or sugar alcohols such as sorbitol, sorbitol syrup, maltitol, maltitol syrup, lactitol, mannitol, xylitol, isomalt, etc., or artificial sweeteners. Examples of intense artificial sweeteners include aspartame, acesulfam K, neohesperidine dihydrochalcone, thaumatin, saccharin, saccharin salts (i.e. sodium saccharin) and cyclamates and cyclamic acid. A single sweetener or a combination of two or more sweeteners may be used. Preferred natural sweeteners are sugar and fructose conveniently used as syrups with 70% solids (on drying), likewise sorbitol as a 70% syrup, and fructooligosaccharides. A particularly preferred combination is aspartame and acesulfam K, e.g. in a 2:1 to 1:2 weight ratio, especially a 0.9:1 to 1:0.9 ratio.

Especially preferred a combination of aspartame, acesulfam and inulin and/or fructooligosaccherides is used as the combination has a synergistic taste effect, relatively effectively mimicking the sweetening effect of sugar and masking any harsh taste of the artificial sweeteners. Fructooligosaccharides can be obtained by partial hydrolysis of inulin and are available under the trade name Raftilose from Orafti SA, Tienen, Belgium, which firm also supplies inulins under the trade name Raftiline. Fructooligosaccharides are also available under the trade name Actilight from Beghin-Meiji Industries, Neuilly-sur-Seine, France. Generally the inulin or fructooligosaccharide will be used in 100-5000 parts by weight per 2 parts by weight of aspartame and acesulfam.

The content of sweetener in the compositions of the invention will depend upon the particular sweeteners used and on whether the composition is to be diluted before consumption. Thus the sweetener content will be chosen so as to give a pleasant sweetness on consumption. Typically the sweetener content will be 0.05 to 1% w/w where intense artificial sweeteners are

used, e.g. about 0.1 to 0.3% w/w. Where natural sweeteners (e.g. invert sugar or fructose) are used, they can typically make up 20-50% w/w, more preferably 30-50% w/w of the overall composition on a dry solids basis.

For compositions intended for adolescents and children not in need of low calorie products, natural sweeteners (e.g. sugar alcohols) and non-carcinogenic sweeteners may be preferred over artificial sweeteners. However, for products intended for calorie-conscious adults, artificial sweeteners may be preferred.

Examples of flavouring agents useful in the compositions of the invention include fruit (e.g. pineapple or citrus) concentrates and concentrated aqueous or non-aqueous flavours such as flavour oils, e.g. citrus oils, for example cold pressed orange oil (B.P.). Orange concentrate, e.g. 65 Brix orange concentrate is particularly suitable. The flavouring agent will be used at a concentration sufficient to give the composition, optionally after dilution, a pleasant taste. By way of example 65 Brix orange concentrate may be used at a concentration of 1 to 20% w/w relative to the total emulsion, preferably 2 to 15% w/w. Alternatively cold pressed orange oil BP may be used at a concentration of 0.04 to 0.3% w/w, preferably 0.06 to 0.2% w/w, relatively to the total emulsion.

It should be recognised that the use of flavours or acidifiers which are soluble in the aqueous phase (e.g. fruit concentrates or citric acid) may affect the solubility of the vitamins in that phase and that it may be necessary in such cases to dilute the aqueous phase to prevent precipitation. Accordingly, acidifiers such as lactic acid and water-insoluble flavours such as citrus oils or water-soluble flavours such as strawberry, raspberry, passion fruit, exotic fruit, peach and apricot flavours and other non-citrus flavours such as pineapple concentrate are preferred.

Where a flavour oil is used, it may be dispersed in the oil phase together with the lipophilic vitamins, or non-vitamin lipophilic drugs, or a combination thereof or alternatively and preferably the flavour and the lipophilic vitamins and/or non-vitamin drugs are separately dispersed in the overall emulsion - in this way any effect of the flavour oil on vitamin stability may be minimized. In these circumstances a phospholipid or another emulsifier is preferably dissolved in the flavour oil and two oil phases, one containing flavour oil and the other containing the lipophilic vitamins and/or non-vitamin lipophilic drugs are intensively mixed with the aqueous phase. This can be done separately (with the two emulsions then being mixed together) or sequentially (with one oil phase, generally the vitamin phase, being intensively mixed with some or all of the aqueous phase and the second oil phase then being intensively mixed with the resulting emulsion (optionally after dilution of this emulsion).

In general the low density of the oils in the disperse phase of an emulsion is one of the major causes of physical instability with a resultant creaming of the emulsion. The density of orange oil, BP is in the range of 0.85 0.88 g/ml and thus much smaller than the density of the bulk aqueous phase which in this case in the range of 1.16 to 1.23 g/ml, for example, 1.16 to 1.19 g/ml. Selecting the appropriate gelling and thickening system thus becomes crucial in order to prevent the separation of the two phases. The gelling and thickening system employed for the formulations in this invention is unique in this respect. This system exhibits gel-sol-gel properties when exposed to shearing stress. The aqueous phase has a gel structure at rest which lock the emulsion droplets in a three-dimensional network of gelling and thickening agents. The emulsion will however flow easily when exposed to only slight stress like turning the bottle upside down or shaking

it. The emulsion will gradually loose viscosity in the mouth and thus will not be perceived as slimy by the consumer.

Suitable preservatives for use in the compositions of the invention include food grade preservatives, for example the potassium and sodium salts of sorbic, benzoic and parahydroxybenzoic acids. Potassium sorbate is especially preferred. The preservative will generally be used at concentrations of 0.05 to 1.5% w/w relative to the total emulsion, preferably 0.1 to 0.3 w/w.

As a colouring agent, beta-carotene may for example be used. Beta-carotene gives the emulsion an orange colour which matches the orange flavour where an orange flavour is used. Beta-carotene as an oily suspension (beta-carotene 30% FS from Roche) or cold-water soluble beta-carotene (beta-carotene 7% CWS from Roche) may be used.

Acidifying agents, e.g. lactic or malic acid, may be included in the compositions of the invention. Lactic acid, available in 80% solution as Purac 80 from Purac biochem bv is preferred. Preferably the pH of the emulsion should be adjusted to below 6, more preferably below 5, e.g. in the range 3 to 5. Where fructooligosaccharides are used in the compositions of the invention, the pH is desirably kept above 4 to avoid hydrolysis.

In a preferred embodiment of the invention, a physiologically tolerable inorganic compound of nanometer size (e.g. 1 to 1000 nm, preferably 5 to 800 nm, especially 10 to 600 nm) is added to the disperse phase of the emulsion in order to further stabilize the oil-water emulsion. The inorganic compound used is desirably of higher density than the oil phase, and preferably of higher density than the aqueous phase too. Suitable inorganic compounds include calcium salts, i.e. calcium carbonate, calcium lactate, calcium gluconate,

calcium citrate, calcium malate, calcium hydroxide and calcium phosphate, preferably calcium carbonate. Other suitable compounds include sodium salts, magnesium salts and zinc salts. Preferably, the inorganic compound is calcium carbonate, which is commercially available in a nanometer size. The inorganic compound thus increases the density of the oil phase, and may if desired be used in quantities sufficient to form an isodense oil-in-water emulsion.

Thus viewed from a further aspect the invention provides a liquid emulsion composition having a continuous aqueous phase containing a gelling agent and a thickener and optionally a physiologically tolerable amount of at least one water soluble vitamin and/or non-vitamin drug, and a discontinuous oil phase comprising at least one lipophilic vitamin and/or non-vitamin drug and optionally an edible triglyceride, said emulsion composition further containing at least one emulsifying agent, preferably one selected from edible phospholipids and fatty acid esters, said oil phase comprising at least one of (i) droplets of a discontinuous aqueous phase containing a physiologically active of beneficial compound dissolved therein, (ii) an inorganic particulate, and (iii) a non-vitamin lipophilic drug compound.

The compositions of the invention are oil-in-water emulsions, preferably with a narrow oil (triglyceride) droplet size distribution with the weight average droplet size (i.e. diameter) (measured for example by light microscopy and comparison with a 1 to 10 μm scale) in the range 1 to 5 μm, more preferably 1 to 4 μm, even more preferably 2 to 4 μm. Emulsification is preferably effected in such a way as to have only a small oversize fraction of droplets, i.e. droplets above 5 μm in diameter. This may be achieved by mixing the aqueous phase and the oil phase using a high intensity mixer, a high speed colloid mill (Koruma, Ytron, Siverson or

Ystral), or a high pressure homogenizer (micro fluidiser) for example a high shear rotor stator mixer, available for example from Ystral GmbH, Dottingen, DE. One example of a suitable mixer is the Diax 600 with a 20G or 20F shaft. An in-line dispersion chamber (e.g. Diax 600, type 22/Z) is preferably used as this can ensure that little or no air is introduced into the emulsion.

It may be more efficient to create an emulsion using only part of the aqueous phase and then to add the emulsion to the remaining portion or portions of the aqueous phase.

On a small scale, the process of the invention preferably involves preparing at least two, and more preferably at least three, aqueous compositions and at least one, preferably two, non-aqueous compositions. The first aqueous composition comprises a solution of a thickening agent (e.g. a vegetable gum or a mixture of vegetable gums, e.g. galactomannans) and a preservative, and a portion of this may be used for the preparation of a pre-emulsion, the remainder being combined with a second aqueous composition which is an aqueous solution of a gelling agent (e.g. agar agar). The vitamin powder mixture and/or non-vitamin drug may be dissolved or dispersed in either of the first or second aqueous solutions or in the combined aqueous composition; preferably however the vitamin powder mixture and/or non-vitamin drug is dispersed in a third aqueous composition, optionally together with further components such as sweeteners, and this third aqueous composition is mixed in with the combined aqueous composition before or preferably after the pre-emulsion is also mixed in. The pre-emulsion of fat soluble vitamins, or non-vitamin lipophilic drugs, or a combination thereof, with optional flavour oils and the aqueous dispersion of vitamins are preferably added to the main solution at a temperature of 24 to 26°C. This ensures that the

potential process loss of vitamins and/or non-vitamin drugs is minimized. Where an oil component such as a flavour oil is used which has the potential to reduce fat-soluble vitamin (especially vitamin A and vitamin D) stability, it is preferred to prepare two oil compositions, a first containing the vitamins and the emulsifier (e.g. a phospholipid) and a second containing an emulsifier (e.g. the same phospholipid) and the further oil component.

In the process of the invention, the gelling agent, for example, agar agar has to be heated in an aqueous medium to above its gel point, for example, 95 to 100°C for agar agar, in order for it to dissolve. However, the vitamins should not be exposed to a temperature higher than 40°C, more preferably not to a temperature above 30°C. Cooling of the liquid gelling agent (e.g. agar agar) solution may be effected by the addition of a further solution, such as sorbitol and/or the thickener solution (guar gum and/or locust bean gum) solutions. During cooling of the gelling agent (e.g. agar agar), thickening agents and bulk sweetener solution, care must be taken to prevent gel formation. The gelling agent (e.g. agar agar) solution has to be cooled through around 32 to 28°C using gentle stirring. Stirring is such that the viscosity does not exceed 3000 cps, preferably 2500 cps, especially 1500 cps, on cooling to 25°C.

The overall volume of water used is preferably kept to the minimum required to keep the vitamins (when present) stably in solution. The proportions of this water used to prepare the different aqueous compositions will generally be selected to be at least the minimum required to produce compositions which can be poured and mixed together, the total desired water content can be made up by addition of water or of aqueous solutions of further components. In this way evaporation losses can be compensated for.

Optionally production and handling is carried out under an inert (e.g. nitrogen or inert (e.g. noble gas)) atmosphere, under a partial vacuum or with nitrogen injection so as to minimize the oxygen contact with the vitamin D, vitamin A and vitamin E. Alternatively oxygen contact may be reduced by preparing the lipophilic vitamin composition and emulsifying this with the thickener solution under an inert atmosphere.

For preparation of emulsions of the inventions, use of a high shear rotor stator mixer or an in-line high speed dispersion rotor stator mixer is preferred.

One preferred embodiment of a small scale preparation of an emulsion according to the invention comprises the following steps:

1. Heat the first batch of water to 60°C.
2. Add agar agar together with potassium sorbate and disperse with high speed mixer.
3. Heat to 95°C to dissolve the agar agar to produce liquid (A).
4. Maintain liquid (A) above the gel point (28-35°C), e.g. at 50°C.
5. Heat a second batch of water to 70°C.
6. Add a 65:35 locust bean gum:guar gum mixture and disperse with a high speed mixer to produce liquid (B).
7. Maintain liquid (B) at a temperature above the gel point of liquid (A), e.g. at 50°C.
8. Remove a fraction, e.g. 5-10% of liquid (B), cool to about 30°C and dilute with water to reduce the viscosity to a level suitable for emulsification and to reduce exposure of the lipophilic vitamins to elevated temperatures. The resultant liquid is liquid (C).
9. Combine the remainder of liquid (B) with liquid (A) and maintain the resulting liquid, liquid (D) above the gel point, e.g. 50°C.
10. Sorbitol solution is added and the temperature

is gradually brought down to 30-35°C.

11. Dexpanthenol is gently heated in a water bath so that it can be easily transferred and then added to the main liquid (D).

12. Add lecithin to DL-α-tocopherol acetate and heat to 50°C to dissolve the lecithin and cool to about 30°C.

13. Add the lipophilic vitamins (e.g. vitamin A, vitamin D, betacarotene and vitamin K) to produce liquid (E).

14. Mix citrus oil (e.g. orange oil) with lecithin and warm slightly, e.g to about 30°C to dissolve the lecithin. The resultant liquid is liquid (F).

15. Add liquid (E) slowly to liquid (C) with a high intensity mixer to produce a pre-emulsion. Then mix in liquid (F) also with a high intensity mixer (i.e. a Diax 600 dispersion machine with a 20G shaft). The resultant pre-emulsion is liquid (G).

16. Mix the vitamin powder mixture (i.e. nicotinamide, thiamine mononitrate, riboflavin, pyridoxine, hydrochloride, folic acid, vitamin B_{12} and sorbitol) together with ascorbic acid and citric acid monohydrate in a batch of water with a high intensity mixer with a dispersion shaft to produce liquid (H).

17. Cool down the main liquid (D) to about 25°C and add liquid (G) and liquid (H). Homogenize the mixtures for 2 minutes with a high intensity mixer with a dispersion shaft taking care not to introduce air into the mixture.

18. Fill resultant mixture into bottles and optionally seal under nitrogen.

The containers used may be single dose containers, e.g. bottles, sachets, vials, etc; however multi-dose

containers are preferred, e.g. 50 to 1000 mL bottles, preferably 500 mL bottles. If the containers are light transmitting, they are preferably brown-coloured, e.g. brown coloured PET. Before the containers are sealed, the head space above the emulsion may if desired be flushed with an oxygen-free gas, e.g. nitrogen.

As mentioned above, deaeration or nitrogen injection is optionally used during the preparation of the emulsion product to exclude oxygen.

Such emulsions may be used directly. Alternatively, such emulsions may conveniently be diluted 1 part with 5 parts by volume of diluent, e.g. tap water or mineral water, milk, fruit juice, or any other alcohol-free beverage. Where water is used the resultant diluted composition may be a clear liquid or a non-clear liquid with an acceptable flavour.

In a further aspect of the invention, the emulsion may be dried, e.g. using conventional spray drying or freeze drying techniques, to form an emulsion concentrate.

Thus viewed from a further aspect the invention provides an emulsion concentrate comprising droplets of an edible oil dispersed in a gelling agent, a thickener and an emulsifying agent, said emulsion concentrate containing at least one lipophilic vitamin.

Viewed from a still further aspect the invention provides a process for the preparation of an emulsion concentrate according to the invention, said process comprising drying, preferably spray drying or freeze drying, a liquid emulsion having a continuous aqueous phase containing a gelling agent and a thickener and a discontinuous edible oil phase, said emulsion further containing at least one emulsifying agent, preferably one selected from edible phospholipids and fatty acid esters.

In one embodiment of the invention, the process comprises drying a liquid emulsion wherein said liquid

emulsion contains in the discontinuous oil phase thereof a non-vitamin lipophilic drug compound.

In a further embodiment of the invention, the process comprises drying a liquid emulsion wherein said liquid emulsion contains in the continuous aqueous phase thereof a non-vitamin drug compound.

In a yet further embodiment of the invention, the process comprises drying a liquid emulsion wherein said liquid emulsion contains in the discontinuous oil phase thereof a non-vitamin lipophilic drug compound, and further contains in the continuous aqueous phase thereof a non-vitamin drug compound.

In one embodiment of the invention the process comprises drying, preferably spray drying or freeze drying, a liquid emulsion wherein lipophilic or hydrophilic vitamins, or other agents (e.g. minerals and/or non-vitamin drugs) are present in particles or droplets (e.g. droplets of deoxygenated aqueous solution) within the oil phase droplets in the emulsion. The particles or droplets may have a small diameter e.g. 1 to 1000 nm, preferably 5 to 800 nm, especially 10 to 600 nm. The particles or droplets would therefore be protected from exposure to oxygen. Thus, dried water-in-oil-in-water and emulsion-in-emulsion emulsions are also compositions according to the invention.

In a preferred embodiment, the process of the invention comprises drying, preferably spray drying or freeze drying, a liquid emulsion, having a physiologically tolerable inorganic compound of nanometer size (e.g. 1 to 1000 nm, preferably 5 to 800 nm, especially 10 to 600 nm), e.g. calcium carbonate particles. These particles serve to stabilise the emulsion. The inorganic compound used is desirably of higher density than the oil phase, and preferably of higher density than the aqueous phase too. Suitable inorganic compounds include calcium salts, i.e. calcium carbonate, calcium lactate, calcium gluconate, calcium

citrate, calcium malate, calcium hydroxide and calcium phosphate, preferably calcium carbonate. Other suitable compounds include sodium salts, magnesium salts and zinc salts. Preferably, the inorganic compound is calcium carbonate, which is commercially available in a nanometer size. An example of such a compound is Calofort® U available from Speciality Minerals. Calofort® U is a precipitated calcium carbonate which consists of ultra-fine calcitic crystals with an average primary particle size of 70 nm. Calcium carbonate has a density of 2.7g/cm^3 and is thus well suited to increase the density of the oil phase to form an isodense oil-in-water emulsion. The inorganic compound thus increases the density of the oil phase, and may if desired be used in quantities sufficient to form an isodense oil-in-water emulsion. Thus an emulsion concentrate containing an inorganic compound of nanometer size is also considered to be a composition according to the invention.

The edible oil used in this regard may for example be or contain an edible triglyceride and/or vitamin E.

The emulsion, which is dried, preferably contains a gelling agent (e.g. agar agar), a thickener (e.g. guar gum and/or locust bean gum) and an emulsifier (preferably selected from edible phospholipids and fatty acid esters, e.g. a phospholipid, such as lecithin.)

Where drying is by freeze drying, the aqueous phase of the emulsion preferably contains at least one water-soluble vitamin and the oil phase preferably contains at least one lipophilic vitamin.

Where drying is by freeze drying, the aqueous phase of the emulsion may comprise concentrated lyophilization aids, e.g. sucrose, sorbitol, lactose, maltodextrin, maltose or mannitol.

Where drying is by spray drying, the emulsion may be vitamin free (or free of vitamins other than vitamin E), with the vitamins being injected into the

atomization zone of the spray drier.

Alternatively, where drying is by spray drying, the emulsion may be vitamin free (or free of water-soluble vitamins), with the vitamins being injected into the atomisation zone of the spray drier. The aqueous phase of the emulsion may comprise a solid carrier e.g. sucrose, sorbitol, lactose or maltodextrin to provide the emulsion concentrate with bulk and mass.

The emulsion concentrate may be reconstituted in water to form an oil-in-water emulsion for consumption or for further dilution before consumption. The emulsion concentrate can be packed into sachets or capsules, compressed into tablets or formulated into any suitable solid dosage form.

Freeze drying can be carried out with the aid of conventional freeze drying equipment such as Steris, Germany or Usi-Froid, France. The freeze drying process for a vitamin, mineral and/or non-vitamin drug emulsion in a small scale preparation will typically involve freeze drying an emulsion with a dry matter (i.e. non-water) content of up to 60% wt, preferably approximately 20% wt. The emulsion is frozen to -80°C and kept at this temperature for 1 to 12 hours. The primary drying is performed by keeping the emulsion for 12 to 144 hours at a pressure of 0.01 to 0.04 hPa, a shelf temperature of -45 to -65°C and a condenser temperature of -80 to -90°C. The secondary drying is performed by increasing the pressure to 0.1 hPa and increasing the shelf temperature to ambient temperature. Secondary drying time is 6 to 24 hours. Freeze drying is terminated by venting the drying chamber with dry nitrogen.

Spray drying is however the preferred technology due to this technology being less expensive and more suitable for high volume products. Spray drying equipment can be supplied from APV Anhydro or GEA Niro A/S, both in Denmark. A spray drying process for a vitamin and/or mineral emulsion will typically involve

spray drying an emulsion with a dry matter (i.e. non-water) content of up to 60% wt, preferably approximately 50% wt, and with a liquid temperature in the range of 30-50°C, preferably 40-50°C, more preferably 30-40°C. An inlet air temperature of 100-180°C (e.g. 160-180°C) in a small scale preparation and 180-250°C in a large scale preparation in both cases with an exhaust or outlet air temperature of 60-100°C (e.g. 60-80°C), or the liquid emulsion is atomised, for example by rotary atomisers at a rotation rate of 20000-35000 rpm or by nozzle atomisers at a pressure of 160-180 bar and with the injection of product fines, vitamin premixture and fine crystals of solid carrier in the atomisation zone. Optionally, particulates, preferably crystalline, more preferably fine crystals, of sucrose, sorbitol, lactose or maltodextrin are also added into the atomisation zone. The emulsion is normally produced with the aid of a high pressure homogenizer or a high intensity mixer with resultant oil droplets having a diameter in the sub-micron range and up to 1-2 μm. The aqueous soluble vitamins and/or minerals may be added as dry ingredients in the form of a premixture and together with product fines or crystals of the solid carrier, for example, sucrose, sorbitol, lactose or maltodextrin into the atomisation zone at the top or bottom of the spray dryer. A co-current, counter-current or mixed flow dryer may be applied. To the spray drying system there may be incorporated a fluid bed at the base of the drying chamber where the aqueous soluble vitamins and/or minerals may be added as dry ingredients in the form of a pre-mixture and together with product fines or crystals of the solid carrier for example, sucrose, sorbitol, lactose or maltodextrin. In both processes loose agglomerate is produced which exhibit good instant and flow properties, i.e. the agglomorate will disperse instantly when mixed with an aqueous diluent.

Doses of the composition of the invention may be

taken between meals or with meals and are suitable for older people with reduced gastric acid secretion.

The compositions of the invention may be used in therapeutic or prophylactic treatment and this forms a further aspect of the invention. Viewed from this aspect the invention provides a method of treatment of a human or non-human mammal subject to combat conditions associated with vitamin deficiency (e.g. beri-beri, nyctalopia, megaloblastic haemopoiesis, pernicious anemia, hypoprothrombis anemia, pellegra, sprue, scurvy, rickets), said method comprising orally administering said subject a composition or supplement according to the invention, optionally following dilution thereof in a physiologically tolerable aqueous liquid.

It will be clear to a person skilled in the art that the compositions, processes and methods of the invention could be extended to the formulation of other food supplements. For example, the composition of the invention could be used to formulate multimineral compositions, combined multivitamin and mineral compositions. Thus, in a preferred embodiment, the compositions of the invention include multiminerals, such as zinc, iron, calcium, iron, iodine, magnesium and phosphorus. Preferably, the minerals are present as inorganic and/or organic salts in the aqueous phase of the composition, for example as calcium lactate, zinc sulphate, potassium iodide, ferrous sulphate and/or magnesium carbonate. Suitable compounds are well known in the art.

Preferably, the minerals are complexed with suitable chelating agents, such as aminopolycarboxylic acids (e.g. EDTA or DTPA) to prevent oxidation of the vitamins in the aqueous phase. Soluble minerals salts may be used in equimolar concentrations with pyrophosphate to give pyrophosphate complexes.

The minerals are optionally present at 15 to 500% RDA, preferably 80 to 120% RDA, as set by the Council

Directive (supra).

Calcium:	800 mg
Phosphorus:	800 mg
Iron:	14 mg
Magnesium:	300 mg
Zinc:	15 mg
Iodine:	150 μg
Copper:	2 mg
Manganese:	1 mg
Chromium:	50 μg
Selenium:	40 μg
Molybdenum:	150 μg

A further aspect of the present invention is to provide kits for reconstituting the emulsion composition of the invention. Viewed from this aspect the invention provides a kit comprising a first container containing a physiologically tolerable aqueous liquid, e.g. water or an aqueous solution, and a second container comprising a concentrate according to the invention, e.g. an emulsion concentrate.

The kits of the invention may also include measuring and/or mixing containers.

The first container may be essentially vitamin and/or mineral and/or non-vitamin drug free. Alternatively it may contain dissolved or dispersed vitamins, and/or minerals. Preferably the first container contains sterile water, optionally with vitamins, minerals, flavours, sweeteners, etc. dissolved therein.

In a further preferred embodiment of the invention, non-vitamin lipophilic drugs can be included in the oil phase of the emulsion and/or hydrophilic non-vitamin drugs can be included in the aqueous phase of the emulsion, together with or in the absence of the lipophilic and/or hydrophilic vitamins.

Viewed from this aspect the invention provides a

pharmaceutical composition in emulsion form comprising a discontinuous oil phase containing an edible oil with optionally dissolved or dispersed therein a non-vitamin drug compound, preferably a lipophilic non-vitamin drug compound or compound mixture, and a continuous aqueous phase containing a gelling agent and a thickener (e.g. guar and/or locust bean gum) and an emulsifying agent (preferably selected from edible phospholipids and fatty acid esters), and optionally a hydrophilic non-vitamin drug compound or compound mixture.

Presentation or formulation of the lipophilic non-vitamin drug compound in this emulsion technology may have the advantage of increasing the bioavailability, particularly oral bioavailability, of a non-vitamin drug, especially a poorly water-soluble drug, due to presentation in an easily-absorbed form such as a dissolved and/or solubilised form. From the gastrointestinal tract the lipophilic non-vitamin drug might be either absorbed the common way into the portal blood or by lympatic absorption. Lympatic absorption is possible because fatty acids and bile salts are present during digestion. The lipophilic non-vitamin drug substance may be absorbed in association with the fatty acid/bile acid micellar phase and therefore be associated in the formation of chylomicrons which are transported into the lymphatic circulation. Through absorption as fat globules into the lymphatic system, the lipophilic non-vitamin drug does not go through any intermediate dissolution stage which is often a rate limiting step for absorption of poorly soluble and lipophilic non-vitamin drugs.

The bioavailability of drugs which are exposed to first pass metabolism in the gastro-intestinal tract or in the liver may be increased due to absorption via the lymphatic system. A further advantage due to the facilitated absorption may be an increase of the absorption rate and thus rapid onset of clinical effect.

Furthermore, the incorporation of the non-vitamin drug substance in the lipid phase of the emulsion might protect the drug molecule from the acid environment in the stomach, and thereby protect the drug from degeneration in the gastric fluid, resulting in an increased bioavailability.

The term drug compound as used herein does not include essential nutrients or their bioprecursors, i.e. vitamins, triglycerides, etc.

Examples of lipophilic non-vitamin drug candidates for the disperse phase and hydrophilic non-vitamin drugs for the aqueous phase particularly relevant for peroral administration are analgesics such as synthetic opioids (e.g. fentanyl, alentanil, sufentanil) and non-steroidal anti-inflammatory drugs (e.g. naproxen, penylbutazone, acetylsalicylic acid). Liquid formulations of anticonvulsants such as carbamazepine, phenytoin and benzodiazepines (e.g. diazepam, clonazepam, midazolam, and nitrazepam), adrenergica (e.g. loratadin and pseudoephedrin, acrivastine and pseudoephdrine) expectorantia/mucolytica (e.g. bromhexin, ammonium chloride, acetyl cysteine, carbocisteine, cocillana, creosote, domidol, guiaphenesin, senega root, terpin hydrate) antitussives (e.g. codein, dextromethorphan, noscapin, ethylmorphine, acetyldihydrocodeine, benzonatate, chlophedianol, clobutinol, dimemorfan, drotebanol, levopropoxyphene, morclofone, thebacon, ziperprol) antihistamines (e.g. acrivastin, cetirizin, ebastine, dexchlorpheniramin, dexbromopheniramin, flunarizine, pizotifen, trimethobenzamide), anti-infectives including antibiotics like penicillins, cephalosporins, beta-lactam antibiotics, aminoglycosides, tetracyclines, chloramphenicol, macrolides, clindamycin, spectinomycin, polymyxin B, colistin, vancomycin, bacitracin, isoniacid, rifampin, ethambutol, streptomycin, pyrazinamide, ethionamide, cycloserine and

aminosalicylic acid, non-opioid analgesics (e.g. paracetamol, acetylsalicylic acid, ibuprofen) are also of value, especially in the treatment of children and elderly. The absorption of a number of other biologically active lipophilic and/or poorly soluble substances may be improved by use of the emulsion technology. Examples of such substances are: Corticosteroids (e.g. hydrocortisone, prednisone, prednisolone), androgens (e.g. testosterone, nandrolone,), progestogens (e.g progesterone, norethisterone, danazol), oestrogens (e.g. megastol, ethinyloestradiol, mestranol), drugs for treatment of Parkinson's disease (e.g. levodopa, carbidopa), anticonvulsants (e.g. carbamazepine, phenytoin), antifungal agents (e.g. griseofulvin, clotrimazole), antibacterials (e.g. nitrofurantoin, sulphapyridine, tetracycline, ceftrioxane), antivirals (e.g. zidovudine), tricyclic antidepressants (e.g. imipramine, amitriptyline) immunosuppressants (e.g cyclosporine A, dihydrocyclosporine D), antineoplastic agents (e.g. 5-fluorouracil, chlorambucil, mercaptopurine, fenretinide), antimalarials (e.g. halofantrine), vasodilators (e.g. cyclandelate), anxientiolytica (e.g. gepirone), antihistamines (e.g. repirinast, cinnarizine, fexofenadine), lipid regulation agents (e.g. probucol), anticoagulantia (e.g. dicuomarol), beta-blockers (e.g. propranolol), therapeutic vitamines (e.g. menatetrenone), antihypertensives (e.g. felodipine, nifedipine, penclomedine), anti protozoal agents (e.g. atovaquone), diuretics (e.g. spironolactone), opioid agonists (e.g. oxycodone), antidepressant (e.g. vanoxerine), antidiabetic agents (e.g. glibenclamide).

Preferred lipophilic drug candidates are Probucol, Diazepam, Danazol, Halofantrine and Cyclosporin A.

Agents for the control of gastric acidity and treatment of peptic ulcers such as cimetidine, ranitidine, famotidine, omeprazole and lansoprazole are

also suitable for use in the compositions of the invention.

Combination products can easily be formulated where the lipophilic non-vitamin drug is contained in the disperse phase while a hydrophilic non-vitamin drug is dissolved in the continuous aqueous phase. Cough and cold formulations are typical common combination products where a cough suppressant is combined with one or two analgesics. Preferred cough and cold drug candidates are dextomethorphan, bromhexin and acetylcystein.

High dosages of drugs can be given due to the flexibility in the dosage volume where up to 10 ml can be given as a single dosage. The possible dosage for a lipophilic non-vitamin drug will depend on the solubility in the disperse phase but may be as high as 500 mg in the case where the drug is a fluid lipid itself. More typically the lipophilic drug will be in the range of sub-micron amounts up to 100 mg. The content of the hydrophilic non-vitamin drug contained in the continuous phase will likewise depend on the aqueous solubility but the available volume for dissolution is larger with a resultant possibility of inclusion of a high amount of active per dosage.

Special emulsion systems like multiple emulsions can also be formulated. A water-in-oil-in-water emulsion (w/o/w) as discussed previously may be suitable where an effective protection of the active ingredient is sought. Peptide hormones like insulin is an example of such case where the hormone needs to be protected from the proteolytic enzymes in the gastro-intestinal during the absorption process.

Viewed from a further aspect, the invention provides a pharmaceutical emulsion according to the invention, said emulsion comprising at least one lipophilic and/or hydrophilic non-vitamin drug, wherein the disperse phase of the emulsion includes a

physiologically tolerable inorganic compound of nanometer size (e.g. 1 to 1000 nm, preferably 5 to 800 nm, especially 10 to 600 nm) to further stabilize the oil-water or water-in-oil-in-water emulsion. The inorganic compound used is desirably of higher density than the oil phase, and preferably of higher density than the aqueous phase too. Suitable inorganic compounds include calcium salts, i.e. calcium carbonate, calcium lactate, calcium gluconate, calcium citrate, calcium malate, calcium hydroxide and calcium phosphate, preferably calcium carbonate. Other suitable compounds include sodium salts, magnesium salts and zinc salts. Preferably, the inorganic compound is calcium carbonate, which is commercially available in a nanometer size. The inorganic compound thus increases the density of the oil phase, and may if desired be used in quantities sufficient to form an isodense oil-in-water emulsion.

The invention will now be described further with reference to the following non-limiting Examples:

EXAMPLE 1

Preparation of a liquid syrup

Ingredients:

Vitamin oil mixture: (6.5g in total)	DL-α-tocopherol acetate	4700 mg
	Vitamin A palmitate	539 mg
	Cholecalciferol concentrate	165 mg
	Lecithin	500 mg
	Medium chain (C_8-C_{12}) tryglycerides	596 mg
Vitamin powder mixture: (10g in total)	Nicotinamide	6.3 mg
	Thiamine nitrate	612 mg
	Riboflavine	550 mg

Pyridoxine hydrochloride	765 mg
Folic acid	45 mg
Sorbitol powder	1728 mg

Dexpanthenol	2 g
Ascorbic acid	28 g
Potassium sorbate:	3.5 g
Sorbitol 70% (non-crystallising):	3.55 kg
Agar agar:	4 g
Sorbitol powder:	54 g
Galactomannan mixture:	17 g
Citric acid monohydrate:	20 g
Orange oil:	3.4 g
Lecithin:	0.3 g
Purified water:	2190 g

A first batch of water is heated to a temperature of 60°C, to which agar agar is added and dispersed with high speed mixer. The mixture is heated to 95°C to dissolve the agar agar to produce liquid (A). Liquid (A) is maintained above the gel point (28-35°C), e.g. at 50°C. A second batch of water is heated to a temperature of 70°C. A 65:35 ratio locust bean gum:guar gum mixture is added and dispersed with a high speed mixer to produce liquid (B). Liquid (B) is maintained at a temperature above the gel point of liquid (A), e.g. at 50°C. A fraction, e.g. 5-10%, of liquid (B) is removed and cooled to about 30°C and diluted with water to reduce viscosity to a level suitable for emulsification. The resultant liquid is liquid (C). The remainder of liquid (B) with liquid (A) are combined and the resulting liquid, liquid (D) is maintained above the gel point, e.g. 50°C. Liquid sorbitol is added and the temperature is gradually brought down to 30-35°C. Dexpanthenol is gently heated in a water bath so that it can be easily transferred and then added to the main liquid (D). Lecithin is added to DL-α-tocopherol

acetate and heated to 50°C to dissolve the lecithin and cooled to about 30°C. The lipophilic vitamins are added (e.g. vitamin A, vitamin D, betacarotene and vitamin K) to produce liquid (E). Citrus oil (e.g. orange oil) is mixed with lecithin and warmed slightly, e.g. to about 30°C to dissolve the lecithin. The resultant liquid is liquid (F). Liquid (E) is added slowly to liquid (C) in a high intensity mixer to produce a pre-emulsion. Liquid (F) is mixed also with a high intensity mixer (i.e. a Diax 600 dispersion machine with a 20G shaft). The resultant pre-emulsion is liquid (G). The vitamin powder mixture (i.e. nicotinamide, thiamine mononitrate, riboflavine, pyridoxine hydrochloride, folic acid and sorbitol) is mixed together with ascorbic acid and citric acid monohydrate in a batch of water in a high intensity mixer with a dispersion shaft to produce liquid (H). The main liquid (D) is cooled to about 25°C and liquid (G) and liquid (H) are added. The mixtures are homogenized for 2 minutes in a high intensity mixer with a dispersion shaft taking care not to introduce air into the mixture. The resultant mixture is filled into bottles and optionally sealed under nitrogen.

The vitamin emulsion is a homogeneous and smooth-flowing yellow or orange coloured syrup with a fresh citrus taste. The syrup has a pH of 3.0 to 3.6, a viscosity of 300 to 1000 cps at 20°C and a density of 1.16 to 1.23 g/ml at 20°C. The diameter of the bulk of the oil droplets in the emulsion is between 2 to 5 μm.

The investigation of viscosity behaviour for the vitamin emulsion was carried out using a stress-controlled instrument called DSR200 from Rheometric Scientific. The first test used was a thixotropy loop test where after mounting, the sample was left for 10 minutes. Then a clockwise rotation of the upper fixture was achieved by ramping the stress from zero to 40 Pa in 10 minutes and then down to 0 Pa in another 10 minutes. After a rest period of 40 minutes the same sequence with

a counter-clockwise rotation was performed.

The second test used was a step stress test where a sequence of stresses was programmed, first in increasing order and then in decreasing order. Each stress was kept constant for a given period. Stresses were applied in the range of 0.06 to 40 Pa in an increasing and descending step-wise fashion.

Results from test one showed that the reproducibility of the clockwise and counterclockwise were good. Only very little hysteresis is seen in ramping the stresses up and down except at the smallest stress values. Therefore the sample shows a thixotropic behaviour only at low stress levels. At higher stress levels (above 30 Pa) structure within the fluid is broken down. A characteristic shear thinning behaviour was evident for the sample.

Results from test two showed that for applied stresses lower than 0.8 Pa (or rates less than 1 s^{-1}) the rotational speed was fluctuating erratically, thus indicating structural changes within the sample as the sample was sheared.

The rheological characterisation showed the presence of thixotropy or a time-dependent decrease in viscosity at low shear stress which is reversible. In other words the emulsion exhibits gel-sol-gel properties. The second test showed the presence of structural rearrangements at small stress levels and the possibility of yield behaviour.

These findings present an explanation to the excellent physical stability of the emulsion and the presence of thixotropy at very low shear stresses (e.g. the emulsion can be poured after shaking the bottle lightly).

EXAMPLE 2

Chemical Stability

A stability study was carried out in order to investigate the chemical stability of the liquid multivitamin product. The product was manufactured according to the protocol set out in Example 1. Two production batches were prepared and subjected to a stability study. The following sampling times were used:

20°C/ambient Relative Humidity (RH): 0, 3, 6, 12 and 18 months

The following results for the vitamin contents after 18 months were obtained for the two production batches respectively at 20°C/ambient RH:

Vitamin	Declared	Overage	Nominal	Initial	Recovery	18 months	Degraded
Retinol (µg/10 ml)	500	10%	550	623, 628	113%	518, 525	16%
Cholecalciferol (µg/10 ml)	7.5	10%	8.25	8.0, 8.1	97.6%	7.3, 7.3	10%
D-α-tocopherol (mg/10 ml)	6.0	5%	6.30	6.2, 6.3	99.2%	6.1, 6.2	2%
Nicotinamide (mg/10 ml)	12	5%	12.6	12.2, 12.3	97.2%	11.6, 11.9	4%
Thiamine (mg/10 ml)	0.9	10%	0.99	0.96, 0.97	97.5%	0.88, 0.89	8%
Riboflavine (mg/10 ml)	1.0	10%	1.10	1.05, 1.06	95.9%	1.08, 1.09	+2%
Pantothenic acid (mg/10 ml)	4.0	10%	4.40	4.3, 4.4	98.9%	3.6, 3.6	16%
Ascorbic acid (mg/10 ml)	45	25%	56.3	54.4, 55.3	97.4%	42.8, 43.6	20%
Pyridoxine (mg/10 ml)	1.2	5%	1.26	1.21, 1.22	96.4%	1.25, 1.24	+2%
Folic acid (µg/10 ml)	75	20%	90.0	92.1, 92.2	102.4%	71.4, 72.5	21%

The initial value for the analysis of retinol is somewhat high which is due to an initial high value of 106% of nominal value in the raw material.

The products have been analyzed with respect to all the vitamins, flavour, appearance, pH, total viable count, test for E.Coli, test for efficacy of anti-microbial preservation, potassium sorbate, viscosity, density and microscopic picture (droplet size of disperse phase).

The initial analysis of the two batches gave vitamin contents very near to the nominal amounts which indicate that there are no detectable loss of vitamin activity during processing.

The lower limit for the vitamin contents for this product is set to 90% of declared amounts. It can be seen that all the vitamins are well inside this limit which shows that the chosen overages for the vitamins are sufficient for a shelf life of 18 months at 20°C and ambient relative humidity.

All the other physical, microbiological and sensoric requirements were according to the required specification when analyzed after 18 months.

EXAMPLE 3

Physical Stability

A stability study was carried out in order to investigate the physical stability of the liquid multivitamin composition. Two production batches referred to in Example 2 were compared with 2 newly produced batches. The four products were all evaluated in the original packaging which is 500 ml polyethylene terephtalate and black coloured bottles.

The earlier produced batches had been stored at 25°C and 60% relative humidity.

The mean oil droplet size and the homogeneity of the

emulsion was investigated by the aid of a Zeiss microscope (Axioskop) with a 40x magnification.

Pictures of the emulsions were taken with the aid of an Olympus DP 10 digital camera and the droplet sizes quantified with Olympus DP-software.

The following procedure was undertaken in order to investigate the homogeneity of the emulsion.

The liquid content of each bottle was poured out into 50 divided doses of 10 ml. The bottles were not shaken before the dispensing of the individual dosages of 10 ml which should represent the most challenging situation with respect to the detection of any emulsion inhomogeneity. The results are presented below.

Results:

Samples were investigated under the microscope in order to evaluate the homogeneity at the top, in the middle and at the bottom of the contents in each bottle. Two separate measurements were carried out on each microscope slide preparation and the number and diameter of the oil droplets from 0.5μm and upwards notified.

The 10 ml samples from each bottle were investigated visually with respect to the presence of any oily film on the surface of the emulsion in each beaker. There was no evidence of an oil film in any of the examined beakers.

All the samples had a homogenous appearance.

The liquid emulsion from all the four batches was easily pourable in a smooth fashion without the presence of any lumps.

There was no evidence of any segregation with respect to the average oil droplet size or the droplet count in the samples taken at the top, middle and bottom of the product in any of the examined batches.

The mean oil droplet size for the four batches was in the range of 3.1 to 6.2 μm. There was no difference between the newly produced batches and the stability

batches with respect to the mean oil droplet size.

There was no evidence of emulsion creaming or phase separation in any of the samples tested and there was no difference in this respect between newly produced batches and batches stored for stability studies at 25°C and 60% relative humidity.

This ensures that the product is homogenous with respect to the dosing of the lipophilic vitamins contained in the discontinuous phase of the product.

EXAMPLE 4

Preparation of 5000 ml of a liquid multivitamin and mineral syrup

Composition:

Vitamin oil mixture:	17.5 g
DL-α-tocopherol acetate:	9600 mg
Vitamin A palmitate:	950 mg
Cholecalciferol concentrate:	540 mg
Betacaroten 20%	1500 mg
Betacaroten 30%	3125 mg
Lecithin:	752 mg
Vitamin powder mixture:	34.84 g
Nicotinamide:	19.2 g
Thiamine nitrate:	1.60g
Riboflavine	1.32g
Pyridoxine hydrochloride:	1.06g
Folic acid:	303 mg
Cyanocobalamin 0.1%:	11.20g
Biotin	109 mg
Dexpanthenol:	9.54 g
Ascorbic acid:	14 g
Sodium ascorbate:	47.03 g
Ferrous sulphate:	52.34 g
Zinc sulphate:	36.88 g

Potassium iodide:	123 mg
Di-sodium-pyrophosphate:	74.06 g
Agar agar:	4.13 g
Galactomannan mixture:	17.34 g
Potassium sorbate:	7.50 g
Apricot flavour:	5.70 g
Fructose:	55 g
Invert sugar:	3350 g
Purified water:	2274 g

The manufacturing method is analogous to that in Example 1 except for the inclusion of the minerals. The di-sodium-pyrophosphate is dissolved in a batch of water and added to the main solution at a temperature of 40-45°C. Ferrous sulphate, zinc sulphate and potassium iodide are added to the same main solution when the temperature has fallen below 40°C.

The function of di-sodium-pyrophosphate is to act as a complexing agent with respect to the minerals. This minimises the metallic aftertase from the minerals and prevents any possible catalytic effect with respect to the degradation of the labile vitamins in solution.

The vitamin and mineral syrup has a fresh taste of apricot, a viscosity of 400-1200 cp at 20°C, density of 1.19-1.23 g/cm^3 and a pH of 3.0-3.5.

Two batches of emulsion were subjected to a stability trial as set out in Example 2 with the results set out in the table below.

The following results for the vitamin contents after 18 months were obtained for the two production batches respectively at 20°C/ambient RH:

Vitamin	Declared	Overage	Nominal	Initial	Recovery	18 months	Degraded
Retinol (IU/5ml)	1500	30%	1950	2145, 2145	110.0%	1869, 1862	13%
Betacaroten (IU/5ml)	1500	30%	1950	2172, 2148	110.8%	2315, 2279	+6.3%
Cholecalciferol (IU/5ml)	400	35%	540	502, 494	92.2%	519, 502	+2.5%
D-α-tocopherol (IU/5ml)	10	20%	12	12.5, 12.4	103.8%	12.0, 11.9	4.0%
Nicotinamide (mg/5ml)	16	20%	19.2	19.5, 19.2	100.8%	18.5, 18.4	4.7%
Thiamine (mg/5ml)	1.0	30%	1.3	1.27, 1.25	96.9%	1.16, 1.16	7.9%
Riboflavine (mg/5ml)	1.2	10%	1.32	1.25, 1.23	93.9%	1.19, 1.19	4.0%
Pantothenic acid (mg/5ml)	6.0	70%	10.2	10.4, 10.3	101.5%	9.2, 9.2	11.1%
Ascorbic acid (mg/5ml)	35	60%	56	53.0, 52.0	93.8%	35.7, 34.9	32.8%
Pyridoxine (mg/5ml)	0.8	10%	0.88	0.88, 0.87	99.4%	0.89, 0.88	+1.1%
Folic acid (µg/5ml)	200	40%	280	276, 266	96.8%	255, 244	7.9%
Biotin (µg/5ml)	100	10%	110	109, 116	102.3%	103, 100	9.8%
Vitamin B_{12} (µg/5ml)	4	180%	11.2	11.6, 11.8	104.5%	9.7, 9.8	16.7%
Iodine (µg/5ml)	90	5%	94.5				
Iron (mg/5ml)	10	5%	10.5	10.9, 10.4	106.5%	10.6, 10.6	0.5%
Zinc (mg/5ml)	8	5%	8.4	8.2, 8.2	102.5%	8.4, 8.2	1.2%

The averages in this example were set somewhat higher when compared to the formulation in Example 1. This was due to the fact that the lower limit for the vitamin contents for this product was set to 100% of declared amounts. It can be seen that all the vitamins are well inside this limit which shows that the chosen overages for the vitamins are sufficient for a shelf-life of 18 months at 20°C and ambient relative humidity.

Indeed the overages for all the vitamins can be reduced to the same levels as chosen in Example 1. Vitamin C is an exception and this overage has to be 60% in order to be 100% of the declared amount at the end of the shelf-life period when stored at 20°C and ambient relative humidity. An overage of 20% is sufficient for vitamin B_{12} in order to ensure the declared amount at the end of the shelf life period (18 months).

All the other physical, microbiological and sensoric requirements were according to the specification when analysed after 18 months.

EXAMPLES 5, 6, 7, 8 AND 9: Variation of Emulsifying Agent

The method of preparation as outlined in Example 1 was followed. The initial viscosity, mean oil droplet size and appearance were recorded.

The formulations were dispensed into 200 ml amber glass bottles and into clear glass test tubes which were capped. The bottles and test tubes were placed in the following conditions: 1) at 7°C and ambient humidity in a refrigerator; 2) 25°C and 60% RH; and 3) 30°C and 60% RH.

The test tubes were observed for any evidence of creaming or coalescence of the disperse phase after 30 days. The samples were also observed to see if any syneresis had taken place. Syneresis is a phenomenon

that can occur in liquid formulations containing a gelling agent. It is thought to be due to changes taking place in the polymer network causing gel shrinkage which results in evolution of a clear aqueous phase devoid of the stabilising gelling and thickening agents. Samples exhibiting syneresis change to a normal homogenous appearance when samples are lightly shaken or bottles turned upside down.

The observations were documented by digital photographs of the test tubes in a cupboard with controlled light conditions.

Five trials were conducted with different types of emulsifying agents. These were Lutrol® F68 or Poloxamer 188 from BASF®, Polysorbate 80 from Dr. W. Kolb AG, Pemulen which is a polyacrylic acid polymer from BFGoodrich Speciality Chemicals, Tefose 1500 which is PEG-6 stearate from Gattefosse and Plurol stearique WL 1009 which is polyglyceryl-6 distearate from Gattefosse.

The emulsifying agent was divided between the oil phase and the aqueous phase in order to ease the dispersion and emulsification process. 100 mg of the emulsifying agent was dispersed in the aqueous phase in the case of Examples 5, 6, 8 and 9 and 50 mg was added to the aqueous phase in case of Example 7.

The composition and analytical results are given below.

Ingredient	5	6	7	8	9
Vitamin oil mixture:					
DL-α-tocopherol acetate	2.82 g	2.82 g	2.82 g	2.82 g	2.82 g
Vitamin A palmitate	324 mg	324 mg	324 mg	324 mg	324 mg
Cholecalciferol concentrate	99 mg	99 mg	99 mg	99 mg	99 mg
Medium chain triglycerides	360 mg	360 mg	360 mg	360 mg	360 mg

Orange oil	2.07 g	2.07 g	2.07 g	2.07 g	2.07 g
Betacaroten susp. 30%	140 mg	140 mg	140 mg	140 mg	140 mg
Polysorbate 80	340 mg				
Poloxamer 188		340 mg			
Pemulen TR-2			98 mg		
Plurol stearique				340 mg	
Tefose 1500					340 mg
Vitamin powder mixture: 6.0g					
Nicotinamide	3.78 g	3.78 g	3.78 g	3.78 g	3.78 g
Pyridoxine hydrochloride	459 mg	459 mg	459 mg	459 mg	459 mg
Thiamine nitrate	367 mg	367 mg	367 mg	367 mg	367 mg
Riboflavine	330 mg	330 mg	330 mg	330 mg	330 mg
Folic acid	29 mg	29 mg	29 mg	29 mg	29 mg
Sorbitol powder	1.04 g	1.04 g	1.04 g	1.04 g	1.04 g
Dexpanthenol	1.236 g	1.236 g	1.236 g	1.236 g	1.236 g
Ascorbic acid	16.89 g	16.89 g	16.89 g	16.89 g	16.89 g
Potassium sorbate	2.1 g	2.1 g	2.1 g	2.1 g	2.1 g
Sorbitol 70% non crystalline	2.13 kg	2.13 kg	2.13 kg	2.13 kg	2.13 kg
Agar	2.44 g	2.44 g	2.44 g	2.44 g	2.44 g
Galactomannan mixture	10.44 g	10.44 g	10.44 g	10.44 g	10.44 g
Sorbitol powder	33.6 g	33.6 g	33.6 g	33.6 g	33.6 g
Citric acid monohydrate	12.18 g	12.18 g	12.18 g	12.18 g	12.18 g
Purified water to:	3000 ml	3000 ml	3000 ml	3000 ml	3000 ml
Viscosity (mPa)	892	1050	1050	964	968
Mean oil droplet size (µn)	2.7	3.2	4.7	3.7	1.9
Mean oil droplet size (µm) 30 days	3.8	3.2	4.1	3.0	3.7

From the results it can be seen, that all the batches contained a disperse phase with a satisfactory low value for the mean droplet size (in the range of 1-5 µm).

Examples 5-9 all showed a satisfactory stability at all temperatures after 30 days. Their mean oil droplet diameter stayed unchanged and there was no evidence of any creaming or syneresis in any of the sample test tubes.

EXAMPLES 10, 11, 12 AND 13: Variation of Gelling Agent

The method of preparation as outlined in Example 1 was followed. The initial viscosity, mean oil droplet size and appearance were recorded.

The formulations were dispensed into 200 ml amber glass bottles and into clear glass test tubes which were capped. The bottles and test tubes were placed in the following conditions: 1) at 7°C and ambient humidity in a refrigerator; 2) 25°C and 60% RH; and 3) 30°C and 60% RH.

The test tubes were observed for any evidence of creaming or coalescence of the disperse phase after 30 days. The samples were also observed to see if any syneresis had taken place. Syneresis is a phenomenon that can occur in liquid formulations containing a gelling agent. It is thought to be due to changes taking place in the polymer network causing gel shrinkage which results in evolution of a clear aqueous phase devoid of the stabilising gelling and thickening agents. Samples exhibiting syneresis change to a normal homogenous appearance when samples are lightly shaken or bottles turned upside down.

The observations were documented by digital photographs of the test tubes in a cupboard with controlled light conditions.

Four trials were conducted with different types of gelling agents in combination with galactomannans gum as

thickener. The gelling agents used were Gelcarin DG 3252 which is an iota carrageenan from FMC Biopolymer, Protanal LF 120M which is a sodium alginate type also from FMC Biopolymer, Genu pectin LM-5 CS which is a low ester pectin from CP Kelco, and Kelcogel LT 100 which is a high acyl gellan gum type from The NutraSweet Kelco Company. 100 mg of the emulsifying agent was dispersed in the aqueous phase in all examples.

The following modifications to the process were carried out in order to dissolve the gelling agent and to facilitate a controlled gelling process. A small amount of calcium ions (0.5-1.2 mM Ca^{2+}) were added to Examples 10-12 in order to facilitate the gelling process. This was not necessary in the case of the gellan gum formulation.

Gelcarin DG 3252 was heated in a batch of water to 70°C where it dissolved. A second batch of water containing the thickener (galactomannan), sorbitol powder, potassium sorbate, and calcium chloride was prepared, and the two solutions were mixed together at a temperature above 70°C. A controlled gelling process took place when liquid sorbitol was added and the temperature was brought below the gelling temperature (60-70°C) for the iota-carrageenan.

Protanal LF 120M was dissolved in a batch of water at room temperature and mixed together with the thickener solution as described above. A controlled gelling took place as the two solutions were mixed together and the temperature was brought down by the subsequent addition of liquid sorbitol.

Genu pectin LM-5 CS is a rapid set low ester pectin with a high calcium reactivity. The gelling agent was heated in a batch of water together with calcium chloride to a

temperature of 90°C. The thickener solution was added as described above and a gelling process initiated as the temperature was reduced by the addition of liquid sorbitol.

Kelcogel LT 100 produces a gelling effect at very low amounts in the presence of mono or divalent ions. The gelling agent was heated in a batch of water to 90°C and the thickener added as in Eample 10. A distinct gelling effect was observed when the temperature was brought down by the addition of liquid sorbitol.

The compositions and analytical results are given below.

Ingredients	10	11	12	13
Vitamin oil mixture: 6,05 g				
DL-α-tocopherol acetate	2.82 g	2.82 g	2.82 g	2.82 g
Vitamin A palmitate	324 mg	324 mg	324 mg	324 mg
Cholecalciferol concentrate	99 mg	99 mg	99 mg	99 mg
Medium chain triglycerides	360 mg	360 mg	360 mg	360 mg
Orange oil	2.07 g	2.07 g	2.07 g	2.07 g
Betacaroten susp. 30%	140 mg	140 mg	140 mg	140 mg
Emultop	240 mg	240 mg	240 mg	240 mg
Vitamin powder mixture: 6,0 g				
Nicotinamide	3.78 g	3.78 g	3.78 g	3.78 g
Pyridoxine hydrochloride	459 mg	459 mg	459 mg	459 mg
Thiamine nitrate	367 mg	367 mg	367 mg	367 mg
Riboflavine	330 mg	330 mg	330 mg	330 mg
Folic acid	29 mg	29 mg	29 mg	29 mg
Sorbitol powder	1.04 g	1.04 g	1.04 g	1.04 g
Dexpanthenol	1.236 g	1.236 g	1.236 g	1.236 g
Ascorbic acid	16.89 g	16.89 g	16.89 g	16.89 g
Potassium sorbate	2.1 g	2.1 g	2.1 g	2.1 g
Sorbitol 70% non crystalline	2.13 kg	2.13 kg	2.13 kg	2.13 kg

Gelcarin DG 3252	3.00 g			
Protanal LF 120M		3.00 g		
Genu pectin LM-5 CS			3.00 g	
Kelcogel LT 100				1.5 g
Galactomannan mixture	10.44 g	10.44 g	10.44 g	10.44 g
Emultop	100 mg	100 mg	100 mg	100 mg
Sorbitol powder	33.6 g	33.6 g	33.6 g	33.6 g
Calcium chloride hexahydrate	600 mg	800 mg	300 mg	-
Citric acid monohydrate	12.18 g	12.18 g	12.18 g	12.18 g
Purified water to:	3000 ml	3000 ml	3000 ml	3000 ml
Viscosity (mPa)	788	408	392	928
Mean oil droplet (μm)	2.9	6.1	3.1	4.3
Mean oil droplet (μm) 30 days	2.7	6.8	3.4	3.2

Examples 10-13 comprising different gelling agents and galactomannan thickener all produced satisfactory emulsions with a viscosity in the range of 300-1000 mPa and a mean oil droplet size of the disperse phase in the range of 2-6 μm.

Examples 10-13 all showed satisfactory stability with respect to the mean droplet size. There was no evidence of either syneresis or creaming in the two formulations containing carrageenan and pectin respectively. The formulation containing gellan gum started to show signs of syneresis for the sample stored at 30 °C. The formulation containing sodium alginate showed signs of creaming and syneresis at both 25 and 30°C. This may be due to an unsuccessful gelling process with a resultant inhomogenous grainy gel.

EXAMPLES 14, 15 AND 16: Variation of Thickener

The method of preparation as outlined in Example 1 was followed. The initial viscosity, mean oil droplet size and appearance were recorded.

The formulations were dispensed into 200 ml amber glass bottles and into clear glass test tubes which were capped. The bottles and test tubes were placed in the following conditions: 1) at 7°C and ambient humidity in a refrigerator; 2) 25°C and 60% RH; and 3) 30°C and 60% RH.

The test tubes were observed for any evidence of creaming or coalescence of the disperse phase after 30 days. The samples were also observed to see if any syneresis had taken place. Syneresis is a phenomenon that can occur in liquid formulations containing a gelling agent. It is thought to be due to changes taking place in the polymer network causing gel shrinkage which results in evolution of a clear aqueous phase devoid of the stabilising gelling and thickening agents. Samples exhibiting syneresis change to a normal homogenous appearance when samples are lightly shaken or bottles turned upside down.

The observations were documented by digital photographs of the test tubes in a cupboard with controlled light conditions.

Three trials have been carried out to investigate different types of thickeners in combination with agar agar. The three thickeners used were Keltrol RD, which is a xanthan gum from Kelco UK Ltd., traganth from Agricales Ltd. and a combination of acacia gum and xanthan gum. 100 mg of the emulsifying agent was dispersed in the aqueous phase in all the examples.

The composition and analytical results are given below.

Ingredients	14	15	16
Vitamin oil mixture: 6,05 g			
DL-α-tocopherol acetate	2.82 g	2.82 g	2.82 g
Vitamin A palmitate	324 mg	324 mg	324 mg
Cholecalciferol concentrate	99 mg	99 mg	99 mg
Medium chain triglycerides	360 mg	360 mg	360 mg
Orange oil	2.07 g	2.07 g	2.07 g
Betacaroten susp. 30%	140 mg	140 mg	140 mg
Emultop	240 mg	240 mg	240 mg
Vitamin powder mixture: 6,0 g			
Nicotinamide	3.78 g	3.78 g	3.78 g
Pyridoxine hydrochloride	459 mg	459 mg	459 mg
Thiamine nitrate	367 mg	367 mg	367 mg
Riboflavine	330 mg	330 mg	330 mg
Folic acid	29 mg	29 mg	29 mg
Sorbitol powder	1.04 g	1.04 g	1.04 g
Dexpanthenol	1.236 g	1.236 g	1.236 g
Ascorbic acid	16.89 g	16.89 g	16.89 g
Potassium sorbate	2.1 g	2.1 g	2.1 g
Sorbitol 70% non crystalline	2.13 kg	2.13 kg	2.13 kg
Agar	2.44 g	2.44 g	2.44 g
Keltrol RD	10.44 g		9.00 g
Traganth gum		7.50 g	
Acacia gum			3.00 g
Sorbitol powder	33.6 g	33.6 g	33.6 g
Emultop	100 mg	100 mg	100 mg
Citric acid monohydrate	12.18 g	12.18 g	12.18 g
Purified water to:	3000 ml	3000 ml	3000 ml
Viscosity (mPa)	1110 mPa	660 mPa	1110 mPa

Mean oil droplet (μm)	2.6	4.5	2.7
Mean oil droplet (μm) 30 days	2.7	3.7	2.6

Examples 14-16 all produced satisfactory results with respect to viscosity and mean oil droplet size of the disperse phase in the ranges of 600-1100 mPa and 2-5 μm respectively.

The stability results for Examples 14-16 after 30 days all showed excellent stability with respect to the mean droplet size and there was no evidence of creaming or syneresis at any temperature.

EXAMPLES 17 AND 18

The method of preparation as outlined in Example 1 was followed. The initial viscosity, mean oil droplet size and appearance were recorded.

The formulations were dispensed into 200 ml amber glass bottles and into clear glass test tubes which were capped. The bottles and test tubes were placed in the following conditions: 1) at 7°C and ambient humidity in a refrigerator; 2) 25°C and 60% RH; and 3) 30°C and 60% RH.

The test tubes were observed for any evidence of creaming or coalescence of the disperse phase after 30 days. The samples were also observed to see if any syneresis had taken place. Syneresis is a phenomenon that can occur in liquid formulations containing a gelling agent. It is thought to be due to changes taking place in the polymer network causing gel shrinkage which results in evolution of a clear aqueous phase devoid of the stabilising gelling and thickening agents. Samples exhibiting syneresis change to a normal homogenous appearance when samples are lightly shaken or

bottles turned upside down.

The observations were documented by digital photographs of the test tubes in a cupboard with controlled light conditions.

Two trials were carried out, each containing a lipophilic drug and an oil phase comprising 5 or 20 %. The drug chosen for exemplification was carbamazepine.

The composition and analytical results are given below.

Ingredients	17	18
Carbamazepine	375 mg	1.5 g
Medium chain triglycerides	144 g	576 g
Betacaroten susp. 30%	1 g	1.5 g
Polysorbate 80	6 g	24 g
Agar	1.83 g	1.83 g
Potassium sorbate	2.1 g	2.1 g
Polysorbate 80	500 mg	500 mg
Galactomannan mixture	7.83 g	5.83 g
Sorbitol 70% non crystalline	2.13 kg	2.13 kg
Sorbitol powder	33.6 g	33.6 g
Emultop	100 mg	100 mg
Citric acid monohydride	12.18 g	12.18 g
Purified water to:	3000 ml	3000 ml
Viscosity (mPa)	632 mPa	1890 mPa
Mean oil droplet size (µm)	5.4	4.4
Mean oil droplet size (µm) 30 days	4.4	4.9

Examples 17 and 18 both showed satisfactory stability with respect to the mean droplet size. The formulation

containing 5% oil phase had a homogenous appearance with no evidence of any creaming or syneresis at the three temperatures. Some syneresis had occurred for the formulation containing 20% oil phase in all three samples. The observed syneresis disappeared when the bottles were shaken lightly.

EXAMPLES 19,20 AND 21: Spray Drying of Liquid Emulsions

Liquid emulsion (A)

Ingredients	mg or µg/10 ml
D-α-tocopheryl acetate	11.0 mg
Vitamin A palmitate 1.7 mill IU/g	1.20 mg
Cholecalciferol concentrate, 1.0 mill IU/g	0.24 mg
Nicotinamide	17.6 mg
Thiamine nitrate	1.28 mg
Riboflavin	1.32 mg
Pyridoxine hydrochloride	1.32 mg
Cyanocobalamin	3.75 mg
Ascorbic acid	78.0 mg
Dexpanthenol	4.31 mg
Sodium benzoate	15.0 mg
Sucrose	6500 mg
Invert syrup 70%	1720 mg
Agar	31.3 mg
Gum traganth	25.0 mg
Lecithin	1.58 mg
Ground nut oil	0.98 mg
Citric acid monohydrate	46.9 mg
Orange oil	15.0 mg
Orange concentrate	97.5 mg
Rose hip extract	85.0 mg
Extract of malt	200 mg
Purified water	4030 mg

Liquid emulsion (B)

Ingredients	mg or µg/10 ml
D-α-tocopheryl acetate	11.0 mg
Vitamin A palmitate 1.7 mill IU/g	1.20 mg
Cholecalciferol concentrate, 1.0 mill IU/g	0.24 mg
Nicotinamide	17.6 mg
Thiamine nitrate	1.28 mg
Riboflavin	1.32 mg
Pyridoxine hydrochloride	1.32 mg
Cyanocobalamin	3.75 mg
Ascorbic acid	78.0 mg
Dexpanthenol	4.31 mg
Sodium benzoate	15.0 mg
Lactose	2000 mg
Aspartame	5.5 mg
Agar	31.3 mg
Gum traganth	25.0 mg
Lecithin	1.58 mg
Ground nut oil	0.98 mg
Citric acid monohydrate	46.9 mg
Orange oil	15.0 mg
Orange concentrate	97.5 mg
Rose hip extract	85.0 mg
Extract of malt	200 mg
Purified water	4030 mg

Liquid emulsion (C)

Ingredients	
D-α-tocopheryl acetate	9.39 mg
Vitamin A palmitate 1.7 mill IU/g	1.08 mg
Cholecalciferol concentrate, 1.0 mill IU/g	0.33 mg
Nicotinamide	12.6 mg
Thiamine nitrate	1.22 mg
Riboflavin	1.10 mg
Pyridoxine hydrochloride	1.53 mg
Folic acid	90.0 µg
Ascorbic acid	56.3 mg
Dexpanthenol	4.12 mg
Potassium sorbate	7.00 mg
Maltodextrin	1000 mg
Aspartame	2.5 mg
Agar	8.12 mg
Galactomannan mixture	34.8 mg
Lecithin	1.60 mg
Triglycerides, medium chain	1.20 mg
Citric acid monohydrate	40.6 mg
Orange oil	6.90 mg
Purified water	4350 mg

Emulsions (A), (B) and (C) are prepared as described in Example 1.

Emulsions (A), (B) and (C) are spray dried in a laboratory spray dryer, Mobil Minor (Niro NS, Denmark). The dryer operates co-currently, has a rotary atomizer and a flow of drying air at approximately 135 kg/h. The inlet air temperature is 120°C, outlet air temperature is held at 75°C, and the rotation rate of the rotary atomizer is 31000 rpm. During spray drying crystals of solid carrier are injected into the atomization zone. After spray drying the emulsion concentrates are stored at ambient temperature in dry condition. The relative

humidity of both the room where the spray drying process takes place and of the inlet air to the spray dryer are low such that the emulsion can be dried to a water content below 1% by weight.

To reconstitute the emulsions, the emulsion concentrates, (A), (B) and (C) are suspended in about 4 g of purified water.

EXAMPLES 22, 23 AND 24: Freeze Drying of Liquid Emulsions

Emulsions (A), (B) and (C) are freeze dried in a laboratory freeze dryer, CD8 freeze dryer (Heto, Denmark). The emulsions are filled into vials (1 ml per vial). The vials are placed on shelves in the freeze dryer and the emulsions are frozen to -80°C and kept at this temperature for 5 hours. Primary drying is performed by keeping the emulsions for 72 hours at a pressure of 0.04 hPa, a shelf temperature of -55°C and a condenser temperature of -90°C. Secondary drying is performed by increasing the pressure to 0.1 hPa and increasing the shelf temperature to 25°C. Secondary drying time is 12 hours. The freeze drying was terminated by venting the drying chamber with dry nitrogen. After freeze drying the emulsion concentrates (A), (B) and (C) were stored at ambient temperature in dry condition.

To reconstitute the emulsions, the emulsion concentrates (A), (B) and (C) are suspended in about 4g of purified water.

EXAMPLE 25

Preparation of a liquid emulsion contaiing a lipophilic drug substances

Composition:

Ingredients	
Probucol	6.00 g
Long chain triglycerides (Soyabean oil)	137 g
Betacaroten susp. 30%	1 g
Polysorbate 80	6 g
Agar	1.83 g
Potassium sorbate	2.1 g
Polysorbate 80	500 mg
Galactomannan mixture	7.83 g
Sorbitol 70% non crystalline	2.13 kg
Sorbitol powder	33.6 g
Emultop	100 mg
Citric acid monohydrate	12.18 g
Purified water to:	3000 ml

The composition is prepared in an analogous manner to Example 1 with the probucol being dissolved in the oil phase by ultrasonification.

EXAMPLE 26

Preparation of a liquid emulsion containing a lipophilic drug substance

Composition:

Ingredients	
Diazepam	3.00 g
Medium chain triglycerides	140 g
Betacaroten susp. 30%	1 g
Polysorbate 80	6 g
Agar	1.83 g
Potassium sorbate	2.1 g
Polysorbate 80	500 mg
Galactomannan mixture	7.83 g
Sorbitol 70% non crystalline	2.13 kg
Sorbitol powder	33.6 g
Emultop	100 mg
Citric acid monohydrate	12.18 g
Purified water to:	3000 ml

The composition is prepared in an analogous manner to Example 1 with the diazepam being dissolved in the oil phase by ultrasonification.

EXAMPLE 27

Preparation of a liquid emulsion contaiing a lipophilic drug substances

Composition:

Ingredients	
Danazol	600 mg
Long chain triglycerides (Soyabean oil)	143 g
Betacaroten susp. 30%	1 g
Polysorbate 80	6 g
Agar	1.83 g
Potassium sorbate	2.1 g
Polysorbate 80	500 mg
Galactomannan mixture	7.83 g
Sorbitol 70% non crystalline	2.13 kg
Sorbitol powder	33.6 g
Emultop	100 mg
Citric acid monohydrate	12.18 g
Purified water to:	3000 ml

The composition is prepared in an analogous manner to Example 1 with the danazol being dissolved in the oil phase by ultrasonification.

EXAMPLE 28

Preparation of a liquid emulsion contaiing a lipophilic drug substances

Composition:

Ingredients	
Halofantrine base	15.0 g
Long chain triglycerides (Peanut oil)	128 g
Betacaroten susp. 30%	1 g
Polysorbate 80	6 g
Agar	1.83 g
Potassium sorbate	2.1 g
Polysorbate 80	500 mg
Galactomannan mixture	7.83 g
Sorbitol 70% non crystalline	2.13 kg
Sorbitol powder	33.6 g
Emultop	100 mg
Citric acid monohydrate	12.18 g
Purified water to:	3000 ml

The composition is prepared in an analogous manner to Example 1 with the halofantrine being dissolved in the oil phase by ultrasonification.

Claims:

1. A process for the preparation of a liquid emulsion composition having a continuous aqueous phase containing a gelling agent and a thickener and optionally a physiologically tolerable amount of at least one water soluble vitamin and/or non-vitamin drug, and a discontinuous oil phase, optionally comprising at least one lipophilic vitamin and/or non-vitamin drug and optionally an edible triglyceride, said emulsion composition further containing at least one emulsifying agent, said process comprising:

forming an aqueous composition comprising an aqueous solution of a gelling agent and a thickener and optionally at least one water soluble vitamin and/or non-vitamin drug;

forming a water-immiscible liquid composition comprising at least one emulsifying agent and optionally at least one lipophilic vitamin and/or non-vitamin drug;

mixing said water-immiscible composition with at least part of said aqueous composition whereby to form an oil-in-water emulsion; and

if required mixing further components with said emulsion whereby to form said liquid emulsion composition.

2. A process for the preparation of an emulsion concentrate comprising forming a liquid emulsion composition by a process as claimed in claim 1 and then drying said liquid emulsion composition.

3. A process for the preparation of an emulsion concentrate comprising spray drying or freeze drying a liquid emulsion having a continuous aqueous phase containing a gelling agent and a thickener and a discontinuous edible oil phase, said emulsion further containing at least one emulsifying agent.

4. A process as claimed in claim 2 or claim 3 wherein drying is effected by spray drying.

5. A process as claimed in claim 4 further comprising the step of adding particulate sucrose or sorbitol into the atomisation zone of the spray dryer.

6. A process as claimed in any one of claims 1 to 5 wherein said liquid emulsion further comprises a solid carrier.

7. A process as claimed in claim 6 wherein said solid carrier comprises sucrose, sorbitol, lactose or maltodextrin.

8. A process as claimed in any preceding claim wherein said gelling agent is selected from agar agar, alginates, carrageenans, gellan gum and pectin.

9. A process as claimed in any preceding claim wherein said thickener is an edible gum or a mixture of edible gums.

10. A process as claimed in any preceding claim wherein said liquid emulsion contains in the discontinuous oil phase thereof a non-vitamin drug compound.

11. A process as claimed in claim 10 wherein said drug compound is a lipophilic drug selected from Probucol, Diazepam, Danazol, Halofantrine and Cyclosporin A.

12. A process as claimed in any one of claims 1 to 10 wherein said liquid emulsion comprises a cough suppressant together with one or more analgesics.

13. A pharmaceutical composition in emulsion form comprising a discontinuous oil phase containing an

edible oil with dissolved or dispersed therein a non-vitamin drug compound or compound mixture, and a continuous aqueous phase containing a gelling agent and a thickener, together with an emulsifying agent.

14. A spray dried emulsion concentrate comprising at least one lipophilic vitamin and/or non-vitamin drug, a gelling agent and a thickener, and optionally an edible triglyceride, further containing at least one emulsifying agent.

15. A freeze dried emulsion concentrate comprising at least one lipophilic vitamin and/or non-vitamin drug, a gelling agent and a thickener, and optionally an edible triglyceride, further containing at least one emulsifying agent.

16. An emulsion concentrate as claimed in claims 14 or 15 wherein said lipophilic vitamin and/or non-vitamin drug is present in the discontinuous phase.

17. A freeze-dried or spray dried emulsion concentrate comprising at least one water-soluble vitamin and/or non-vitamin drug, a gelling agent and a thickener, and optionally an edible triglyceride, further containing at least one emulsifying agent.

18. An emulsion concentrate as claimed in claims 14 or 15 wherein said water-soluble vitamin and/or non-vitamin drug is present in the aqueous phase.

19. An emulsion concentrate comprising droplets of an edible oil dispersed in a gelling agent, a thickener and an emulsifying agent, said emulsion concentrate containing at least one lipophilic vitamin.

20. A kit comprising a first container containing a

physiologically tolerable aqueous liquid, and a second container containing an emulsion concentrate as claimed in any one of claims 14 to 19.

21. An emulsion composition comprising a continuous aqueous phase and a discontinuous oil phase which contains a particulate solid at a concentration such that said phases are isodense.

22. A liquid emulsion composition having a continuous aqueous phase containing a gelling agent and a thickener and optionally a physiologically tolerable amount of at least one water soluble vitamin and/or non-vitamin drug, and a discontinuous oil phase optionally comprising at least one lipophilic vitamin and/or non-vitamin drug and optionally an edible triglyceride, said emulsion composition further containing at least one emulsifying agent, said oil phase comprising at least one of (i) droplets of a discontinuous aqueous phase containing a physiologically active or beneficial compound dissolved therein, (ii) an inorganic particulate, and (iii) a non-vitamin lipophilic drug compound.

23. An emulsion composition as claimed in claim 22 wherein said non-vitamin lipophilic drug compound is selected from Probucol, Diazepam, Danazol, Halofantrine and Cyclosporin A.

24. An emulsion composition as claimed in claim 22 which comprises a cough suppressant together with one or more analgesics.

25. A method of treatment of a human or non-human mammal subject to combat conditions associated with vitamin deficiency (e.g. beri-beri, nyctalopia, megaloblastic haemopoiesis, pernicious anemia, hypoprothrombis anemia, pellegra, sprue, scurvy,

rickets), said method comprising orally administering to said subject a composition or emulsion concentrate as claimed in any one of claims 13 to 19, 21 and 22, optionally following dilution thereof in a physiologically tolerable aqueous liquid.

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(74) Agents: **COCKBAIN, Julian** et al.; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK (utility model), SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/024165 A3

(54) Title: PREPARATION OF VITAMIN EMULSIONS AND CONCENTRATES THEREOF

(57) Abstract: The invention provides a process for the preparation of a liquid emulsion composition having a continuous aqueous phase containing a gelling agent and a thickener and optionally a physiologically tolerable amount of at least one water soluble vitamin and/or non-vitamin drug, and a discontinuous oil phase, optionally comprising at least one lipophilic vitamin and/or non-vitamin lipophilic drug and optionally an edible triglyceride, said emulsion composition further containing at least one emulsifying agent, said process comprising: forming an aqueous composition comprising an aqueous solution of a gelling agent and a thickener and optionally at least one water soluble vitamin and/or non-vitamin drug; forming a water-immiscible liquid composition comprising at least one emulsifying agent and optionally at least one lipophilic vitamin and/or non-vitamin drug; mixing said water-immiscible composition with at least part of said aqueous composition whereby to form an oil-in-vater emulsion; and if required mixing further components with said emulsion whereby to form said liquid emulsion composition.

INTERNATIONAL SEARCH REPORT

al Application No
PCT/GB 01/04231

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/107 A61K9/00 A23L1/302 A23L1/22 A61K31/5513
A61P03/02 A61K31/55 A61K31/10 A61K31/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 192 577 A (MASSON GERARD) 9 March 1993 (1993-03-09) column 1, paragraph 4 - paragraph 5 column 2, paragraph 5 - paragraph 6 column 3, paragraph 2 column 3, last paragraph -column 4, paragraph 3 column 5, paragraph 3; claims 1,3,7,8,13,17-19; example 3 ---	1,8,9, 13,22,25
X	EP 0 972 513 A (EISAI CO LTD) 19 January 2000 (2000-01-19) page 2, paragraph 1 page 2, paragraph 9 - paragraph 10 page 2, last paragraph page 3, paragraph 14 - paragraph 15; claims 2,5,9; example 2 --- -/--	1-4,6-9, 14,16, 19,22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 September 2002	-4 10. 2002
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Marttin, E

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 919 193 A (SHINSHIRO OHTAKI) 20 February 1963 (1963-02-20) page 1, column 1, paragraph 3 - last paragraph page 1, column 2, paragraph 2; claims 1,2; example 2	1-4,9, 13,16, 19,22
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1993 JIZOMOTO HIROAKI ET AL: "Gelatin-acacia microcapsules for trapping micro oil droplets containing lipophilic drugs and ready disintegration in the gastrointestinal tract." Database accession no. PREV199396115711 XP008005312 abstract & PHARMACEUTICAL RESEARCH (NEW YORK), vol. 10, no. 8, 1993, pages 1115-1122, ISSN: 0724-8741	1,2,6, 9-11,13, 22,23
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X	US 4 497 800 A (LARSON DALMON M ET AL) 5 February 1985 (1985-02-05) column 4, line 52 - line 66 column 6, line 23 - line 34 column 6, line 55 -column 8, line 10; claims 1,13,14	13,22,25
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 04598 A (BETATENE LTD) 18 March 1993 (1993-03-18) page 1, paragraph 2 page 3, paragraph 2 - last paragraph page 5, paragraph 3 - paragraph 5 page 6, paragraph 4 -page 7, paragraph 1; claims 1,10,11,13,19,22-25,28-31,33,35,37,38,48; example 1	1,6-13, 22-25
P,X	WO 00 54838 A (NYCOMED PHARMA AS ;PIENE JAN YNGVAR (NO)) 21 September 2000 (2000-09-21) page 1, paragraph 1 page 2, paragraph 6 -page 3, paragraph 1 page 7, last paragraph -page 8, paragraph 1 page 11, paragraph 4 page 12, last paragraph -page 14, paragraph 2	1,6, 8-10,13, 19,20, 22,25
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X	US 5 393 461 A (FILLIPOVA IRINA V) 28 February 1995 (1995-02-28) column 1, line 64 -column 2, line 27 column 2, line 43 - line 55 column 3, line 42 -column 4, line 44; example 3	21,22
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 1 077 059 A (BEIERSDORF AG) 21 February 2001 (2001-02-21) page 2, line 3 - line 5 page 2, line 49 - line 51 page 5, line 31 - line 38 page 6, line 49 -page 7, line 9 page 10, line 11 - line 13 page 13, line 22 - line 24 page 14, line 20 - line 36 page 16, line 35 - line 50; claims 1,9,11; examples	21,22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 01/04231

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 25 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-20, 22-25 partially

A liquid emulsion with a continuous aqueous phase, containing a gelling agent and a thickener, a discontinuous oil phase and an emulsifying agent, and an emulsion concentrate containing a gelling agent, a thickener and a emulsifying agent. And a method of treatment to combat conditions associated with vitamin deficiency comprising orally administering such an emulsion and emulsion concentrate.

2. Claims: 21, 22-25 partially

An emulsion comprising a continuous aqueous phase and a discontinuous oil phase, which contains a particulate. And a method of treatment to combat conditions associated with vitamin deficiency comprising orally administering such an emulsion concentrate.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/04231

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